8 First Trimester Evaluation

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In the last 30 years, the first trimester scan has evolved from an examination for the assessment of fetal viability and gestational age to become the central component of an integrated clinic for the diagnosis of fetal abnormalities and assessment of risk for a wide range of pregnancy complications. This chapter reviews the accumulated data on the role of the first trimester scan in pregnancy care.

SCREENING FOR FETAL ANEUPLOIDIES

Aneuploidies are major causes of perinatal death and childhood handicap. Consequently, the detection of chromosomal disorders constitutes the most frequent indication for invasive prenatal diagnosis. However, invasive testing, by amniocentesis or chorionic villous sampling, is associated with a risk of miscarriage, and therefore these tests are carried out only in pregnancies considered to be at high risk for aneuploidies.[1]

In the last 40 years, prenatal screening for aneuploidies has focused on trisomy 21. The method of screening has evolved from maternal age in the 1970s with a detection rate (DR) for trisomy 21 of 30% and a false positive rate (FPR) of 5%, to a combination of maternal age and second trimester serum biochemistry in the 1980s and 1990s, with a DR of 60% to 70% and a FPR of 5%. In the last 20 years, a combination of maternal age, fetal nuchal translucency (NT) thickness, and serum-free β-hCG and PAPP-A in the first trimester has been advocated, with a DR of 90% and a FPR of 5%.[2] Studies in the last 10 years have shown that improvement in the performance of first trimester screening can be achieved by inclusion in the ultrasound assessment of the nasal bone, flow in the ductus venosus, hepatic artery, and across the tricuspid valve.

A beneficial consequence of screening for trisomy 21 is the early diagnosis of trisomies 18 and 13, which are the second and third most common chromosomal abnormalities, with a relative prevalence to trisomy 21 at 11 to 13 weeks' gestation of 1:3 and 1:7, respectively.[3,4] Since all three trisomies are similar in being associated with increased maternal age, increased fetal NT, and decreased serum PAPP-A, screening using the algorithm for trisomy 21 can detect about 90% of cases of trisomy 21 and 70% to 75% of cases of trisomies 18 and 13, at FPR of 4% to 5%.[5,6] However, with the use of specific algorithms for each trisomy, which incorporate not only their similarities but also their differences in biomarker pattern, including high serum-free β-hCG in trisomy 21 and low levels in trisomies 18 and 13 and high fetal heart rate in trisomy 13, it is possible to increase the DR of trisomies 18 and 13 to about 95% at the same overall FPR of about 4% to 5%.[5,6]

In addition to trisomies 21, 18, and 13, invasive testing in the screen positive group from the combined test detects many other clinically significant aneuploidies.[7] However, the biomarker profile for many of the rare aneuploidies and chromosomal imbalance syndromes is not clearly defined, and it is uncertain whether their incidence in the screen positive group for trisomy 21 is higher than in the screen negative group. The only exceptions are monosomy X, presenting with large fetal NT, and triploidy presenting with either very high serum-free β-hCG and large NT or very low serum-free β-hCG and PAPP-A.[2,8–10]

Several studies in the last 3 years have reported the clinical validation and implementation of screening for aneuploides by analysis of cell-free (cf) DNA in maternal blood.[11] Most studies have reported on screening for trisomies 21, 18, and 13, and a few have also reported diagnostic accuracy in sex chromosome aneuploidies. Some proof of principle studies have examined the potential value of cfDNA testing in the detection of triploidy, trisomies other than those affecting chromosomes 21, 18, and 13, and chromosomal deletions and duplications.[12–14] The combined data from studies involving a large number of affected and unaffected pregnancies indicate that with cfDNA analysis the DR for trisomies 21, 18, and 13 and monosomy X is 99.0%, 96.8%, 92.1%, and 88.6%, respectively, at FPR of 0.08%, 0.15%, 0.20%, and 0.12%.[11]

Nuchal Translucency Thickness

NT is the sonographic appearance of a collection of fluid under the skin behind the fetal neck in the first trimester of pregnancy.[15] The term translucency is used, irrespective of whether it is separated or not and whether it is confined to the neck or envelopes the whole fetus. The incidence of chromosomal and other abnormalities is related to the size, rather than the appearance of NT.[16] During the second trimester, the translucency usually resolves and, in a few cases, it evolves into either nuchal edema alternatively referred to as increased nuchal thickness in the mid-trimester or cystic hygromas with or without generalized hydrops.

Measurement of Nuchal Translucency Thickness

The optimal gestational age for measurement of fetal NT is 11^{+0} to 13^{+6} weeks. The minimum fetal crown rump length (CRL) should be 45 mm and the maximum 84 mm. The lower limit is selected to allow the sonographic diagnosis of many major fetal abnormalities, which would have otherwise been missed, and the upper limit is such as to provide women with affected fetuses the option of an earlier and safer form of termination. Fetal NT can be measured by either transabdominal or transvaginal sonography, and the results are similar. When measuring the NT, the magnification of the image should be such that the fetal head and upper thorax occupy the whole screen, and a midsagittal section of the fetus in a neutral position must be obtained (Fig. 8.1). The widest part of translucency must always be measured, and care must be taken to distinguish between fetal skin and amnion. Measurements should be taken with the inner border of the horizontal line of the calipers placed on the line that defines the NT thickness—the crossbar of the calipers should be such that it is hardly visible as it merges with the white line of the border, not in the nuchal fluid. During the scan, more than one measurement must be taken, and the maximum one that meets all the above criteria should be recorded.

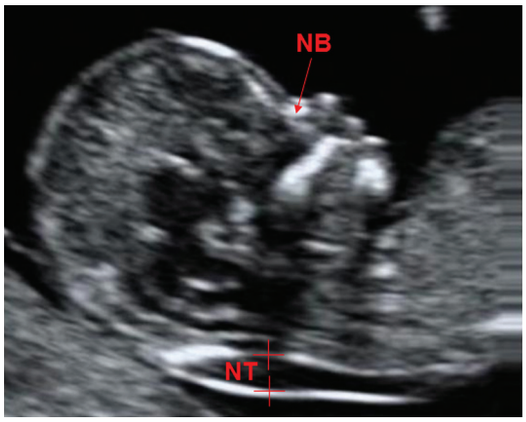

FIGURE 8.1: Ultrasound picture of a fetus at 12 weeks' gestation illustrating the measurement of nuchal translucency *(NT)* thickness and assessment of the nasal bone *(NB)*.

Implications of Increased Nuchal Translucency Thickness

The measurement of fetal NT thickness provides effective and early screening for trisomy 21 and other major aneuploidies.[17–19] Furthermore, high NT is associated with fetal death, cardiac defects, and a wide range of other fetal malformations and genetic syndromes.[20–24] The heterogeneity of conditions associated with increased NT suggests that there may not be a single underlying mechanism for the collection of fluid under the skin of the fetal neck. Possible mechanisms include cardiac dysfunction in association with abnormalities of the heart and great arteries, venous congestion in 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.

In normal fetuses NT thickness increases with fetal CRL. The median and 95th percentile of NT at a CRL of 45 mm are 1.2 and 2.1 mm, and the respective values at CRL of 84 mm are 1.9 and 2.7 mm. The 99th percentile does not change significantly with CRL, and it is about 3.5 mm. Increased NT refers to a measurement above the 95th percentile.

The prevalence of fetal abnormalities and adverse pregnancy outcome increases exponentially with NT thickness (Table 8.1). However, the parents can be reassured that the chances of delivering a baby with no major abnormalities are more than 90% if the fetal NT is between the 95th and 99th centiles, about 70% for NT of 3.5 to 4.4 mm, 50% for NT 4.5 to 5.4 mm, 30% for NT of 5.5 to 6.4 mm, and 15% for NT of 6.5 mm or more.

Management of Pregnancies with Increased Nuchal Translucency Thickness

In pregnancies with fetal NT below the 99th percentile (3.5 mm), the decision by the parents in favor of or against fetal karyotyping will depend on the patient-specific risk for chromosomal defects, which is derived from the combination of maternal age, sonographic findings, and serum-free β-hCG and PAPP-A. In terms of the subsequent management of the pregnancy, it would be best to carry out a detailed fetal scan at 20 weeks to determine fetal growth and diagnose or exclude major abnormalities that could not be identified at the 11 to 13^{+6} weeks scan.

A fetal NT above 3.5 mm is found in about 1% of pregnancies. The risk of major chromosomal abnormalities is very high and increases from about 20% for NT of 4.0 mm to 33% for NT of 5.0 mm, 50% for NT of 6.0 mm, and 65% for NT of 6.5 mm or more. Consequently, the first line of management of such pregnancies should be the offer of fetal karyotyping by CVS. In the chromosomally normal group, a detailed scan, including fetal echocardiography, should be attempted between 14 and 16 weeks to determine the evolution of the NT and to diagnose or exclude many fetal defects. If this scan demonstrates resolution of the NT with normal nuchal thickness measurement in the mid-trimester and absence of any major abnormalities, the parents can be reassured that the prognosis is likely to be good and the chances of delivering a baby with no major abnormalities is more than 95%. The only necessary additional investigation is a detailed scan at 20 to 22 weeks for the exclusion or diagnosis of both major abnormalities and the more subtle defects that are associated with certain associated genetic syndromes. If none of these is found, the parents can be counseled that the risk of delivering a baby with a serious abnormality or neurodevelopmental delay may not be higher than in the general population.

Persistence of unexplained increased NT at 14 to 16 weeks scan or evolution to nuchal edema or hydrops fetalis at 20 to 22 weeks raises the possibility of congenital infection or a genetic syndrome. Maternal blood should be tested for toxoplasmosis,

Table 8.1 Relation between Nuchal Translucency Thickness and Prevalence of Chromosomal Defects, Miscarriage or Fetal Death, and Major Fetal Abnormalities

Nuchal Translucency	Chromosomal Defects (%)	Fetal Death (%)	Major Fetal Abnormalities (%)	Alive and Well[a] (%)
<95th centile	0.2	1.3	1.6	97
95th–99th centiles	3.7	1.3	2.5	93
3.5–4.4 mm	21.1	2.7	10.0	70
4.5–5.4 mm	33.3	3.4	18.5	50
5.5–6.4 mm	50.5	10.1	24.2	30
≥6.5 mm	64.5	19.0	46.2	15

[a]Estimated prevalence of delivery of a healthy baby with no major abnormalities.

cytomegalovirus, and parvovirus B19. Follow-up scans to define the evolution of the edema should be carried out every 4 weeks. Additionally, consideration should be given to DNA testing for certain genetic conditions, such as spinal muscular atrophy, even if there is no family history for these conditions. In pregnancies with unexplained nuchal edema at 20 to 22 weeks scan, the parents should be counseled that there is up to a 10% risk of evolution to hydrops and perinatal death or a live birth with a genetic syndrome, such as Noonan syndrome. The risk of neurodevelopmental delay is estimated at 3% to 5%.

Additional Ultrasound Markers

At 11 to 13 weeks absence of the fetal nasal bone, reversed a-wave in the ductus venosus, tricuspid regurgitation, and increased peak systolic velocity (PSV) in the hepatic artery are observed in about 60%, 66%, 55%, and 80% of fetuses with trisomy 21 and in 2.5%, 3.0%, 1.0%, and 5%, respectively, of euploid fetuses.[25–34]

Absent or Hypoplastic Nasal Bone

In the assessment of the nasal bone at 11 to 13 weeks scan, a midsagittal view of the fetal profile should be obtained, and the magnification of the image should be such that the head and upper thorax occupy the whole screen. The ultrasound transducer should be parallel to the direction of the nose, and the probe must be gently tilted from one side to the other of the fetal nose. The exact midsagittal plane of the fetal face is defined by the echogenic tip of the nose and rectangular shape of the palate anteriorly, the translucent diencephalon in the center, and the nuchal membrane posteriorly.

When these criteria are satisfied, it will be possible to visualize at the level of the fetal nose three distinct lines. Two of them, proximal to the forehead, will be horizontal and parallel to each other, resembling an "equal sign." The top line represents the skin and the bottom one, usually thicker and more echogenic than the overlying skin, represents the nasal bone (see Fig. 8.1). The nasal bone is considered to be present if it is more echogenic than the overlying skin and absent if it is either not visible or its echogenicity is the same or less than that of the skin.

Abnormal Flow Across the Ductus Venosus

The ductus venosus is a short vessel connecting the umbilical vein to the inferior vena cava that plays a critical role in preferentially shunting oxygenated blood to the fetal brain. About 20% of oxygenated blood from the placenta bypasses the liver and is directed to the heart. It enters the right atrium and then is shunted across the foramen ovale into the left atrium. From the left atrium, the blood passes into the left ventricle and then the aorta. The ductus venosus usually closes within a few minutes after birth but this may take longer in preterm neonates.

Increased impedance to flow in the fetal ductus venosus at 11 to 13 weeks' gestation is associated fetal aneuploidies, cardiac defects, and other adverse pregnancy outcomes.[29,35–39] Blood flow in the ductus venosus has a characteristic waveform with high velocity during ventricular systole (S-wave) and diastole (D-wave) and forward flow during atrial contraction (a-wave). Most studies examining ductus venosus flow have classified the waveforms as normal, when the a-wave observed during atrial contraction is positive, or abnormal, when the a-wave is absent or reversed. The preferred alternative in the estimation of patient-specific risks for pregnancy complications is measurement of the pulsatility index for veins (PIV) as a continuous variable.[40]

In the assessment of ductus venosus flow, a right ventral midsagittal view of the fetal trunk should be obtained and the magnification of the image should be such that the fetal thorax and abdomen occupy the whole screen (Fig. 8.2). The examinations should be undertaken during fetal quiescence and color flow mapping must be used to demonstrate the umbilical vein, ductus venosus, and fetal heart. The pulsed Doppler sample should be small (0.5 to 1.0 mm) to avoid contamination from the adjacent veins and it must be placed in the yellowish aliasing area, the insonation angle should be less than 30°, the filter should be set at a low frequency (50 to 70 Hz) to allow visualization of the whole waveform and the sweep speed should be high (2 to 3 cm per second) so that the waveforms were widely spread. The ductus venosus PIV is measured by the machine after manual tracing of the outline of the waveform.

Tricuspid Regurgitation

Tricuspid regurgitation at 11 to 13 weeks' gestation is a common finding in fetal aneuploidies and major cardiac defects.[30–32,41]

In the assessment of tricuspid flow, an apical four-chamber view of the fetal heart should be obtained and the magnification of the image should be such that the fetal thorax occupies the whole screen. The pulsed Doppler sample should be large (2.0 to 3.0 mm) and positioned across the tricuspid valve, the

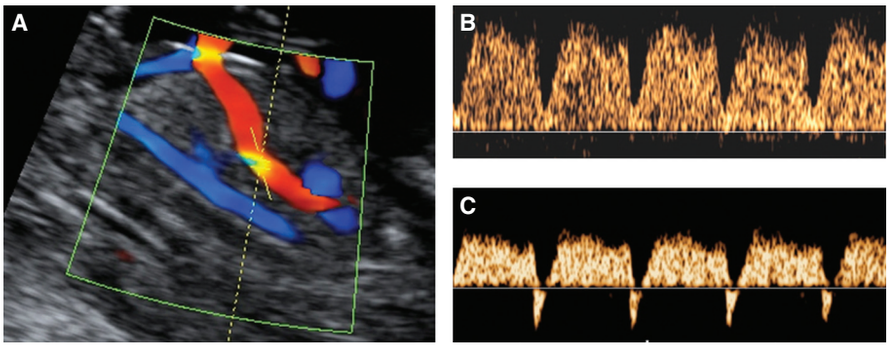

FIGURE 8.2: Midsagittal view of the fetal trunk demonstrating insonation of the ductus venosus **(A)** of a fetus at 12 weeks with normal waveform **(B)** and reversed a-wave **(C)**.

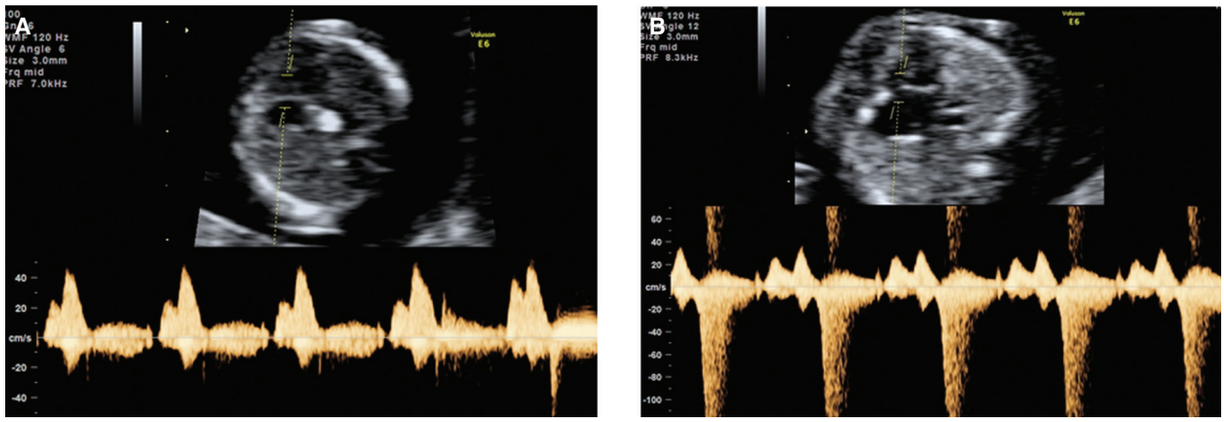

FIGURE 8.3: Transverse view of the fetal heart demonstrating Doppler assessment of flow across the tricuspid valve of a fetus at 12 weeks with normal waveform **(A)** and tricuspid regurgitation **(B)**.

insonation angle to the direction of flow should be less than 30° from the direction of the interventricular septum, and the sweep speed should be high (2 to 3 cm per second) so that the waveforms are widely spread (Fig. 8.3). The tricuspid valve could be insufficient in one or more of its three cusps, and therefore the sample volume should be placed across the valve at least three times, in an attempt to interrogate the complete valve. Tricuspid regurgitation is diagnosed, if it is found during at least half of the systole and with a velocity of over 60 cm per second, since aortic or pulmonary arterial blood flow at this gestation can produce a maximum velocity of 50 cm per second.

Increased Blood Velocity in the Hepatic Artery

In fetal life, the liver is a vital organ with both metabolic and hemopoietic activities. Normally, more than 90% of the blood supply to the liver is from the umbilical and portal veins and less than 10% comes directly from the hepatic artery that is a branch of the celiac trunk from the descending aorta. In trisomy 21 fetuses at 11 to 13 weeks' gestation, the fetal hepatic artery PSV is increased and the PI is decreased.[33,34]

In the assessment of hepatic artery flow, a right ventral midsagittal view of the fetal trunk should be obtained and the magnification of the image should be such that the fetal thorax and abdomen occupy the whole screen. The examinations should be undertaken during fetal quiescence and color flow mapping should be used to demonstrate the umbilical vein, ductus venosus, descending aorta, and hepatic artery (Fig. 8.4). The pulsed Doppler sample must be set at 2.0 mm and placed so that it includes both the ductus venosus and the adjacent upper part of the hepatic artery (to ensure that this vessel rather than the celiac trunk is sampled) and it should then be reduced to 1.0 mm to include only the hepatic artery. The insonation angle to the hepatic artery must be less than 30°, the filter should be set at a high frequency (120 Hz) to avoid contamination from adjacent veins, the sweep speed should be high (2 to 3 cm per second) so that the waveforms are widely spread, and the pulsed wave pulse repetition frequency should be adjusted allowing better assessment of the PSV. When three similar consecutive waveforms are obtained, the PSV and PI are measured by the software of the machine after manual tracing.

Clinical Implementation

In first trimester combined screening, each of the additional ultrasound markers can be assessed in all patients resulting in an increase in DR from 93% to 96% and a decrease in FPR

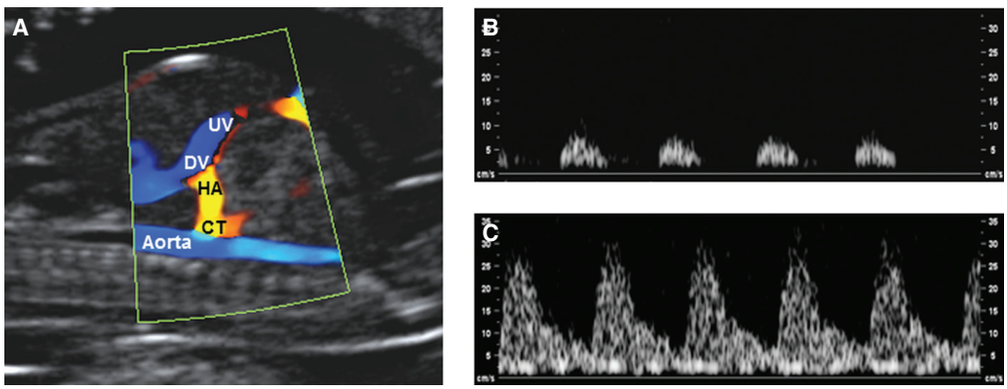

FIGURE 8.4: **A:** Right ventral midsagittal view of a fetus at 12 weeks demonstrating the umbilical vein *(UV)*, ductus venosus *(DV)*, descending aorta, hepatic artery *(HA)*, and celiac trunk *(CT)*. The peak systolic velocity in the waveform from the fetus with trisomy 21 **(C)** is much higher than in a euploid fetus **(B)**.

to less than 3%. A similar performance of screening can be achieved by a contingent policy in which first-stage screening by maternal age, fetal NT, and serum-free β-hCG and PAPP-A is offered to all cases (Fig. 8.5).[42] Patients with a risk of 1 in 50 or more are considered to be screen positive and those with a risk of less than 1 in 1,000 are screen negative. Patients with the intermediate risk of 1 in 51 to 1 in 1,000, which constitutes 15% to 20% of the total population, have second-stage screening with nasal bone, ductus venosus, or tricuspid blood flow that modifies their first-stage risk. If the adjusted risk is 1 in 100 or more, the patients are considered to be screen positive and those with a risk of less than 1 in 100 is screen negative.

Screening in Twins

The first step in screening for trisomies in twins is to determine chorionicity by ultrasound at 11 to 13 weeks (Fig. 8.6).[43] In monochorionic twins, the average of the two NT measurements can be used to calculate the pregnancy risk and in dichorionic twins, the individual NT measurements can be used to calculate the fetus-specific risk.[44,45] Measurement of serum-free β-hCG and PAPP-A is also useful in screening for trisomies in twins, but it is important to make the necessary adjustments because the levels change with gestation and they are lower in monochorionic than in dichorionic pregnancies.[46–48]

In twins, the DR of trisomy 21 by the combined test is about 90% but at a higher FPR than in singletons (6% vs. 5%).[44] In monochorionic twins, the FPR is even higher, at about 9%, because increased NT in one of the fetuses may be an early sign of twin-to-twin transfusion syndrome, rather than trisomy.[44]

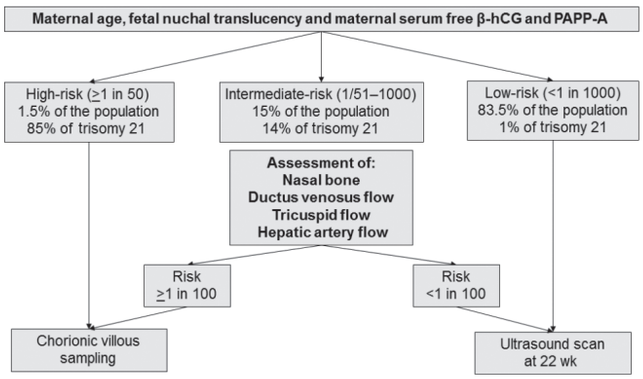

FIGURE 8.5: Two-stage screening for fetal aneuploidies. In the first stage, all patients have screening by a combination of maternal age, fetal nuchal translucency thickness, and maternal serum-free β-hCH and PAPP-A, and according to the results they are classified into high-risk, intermediate-risk, and low-risk groups. In the intermediate-risk group, second-stage screening is carried out by one or more sonographic markers, including nasal bone, blood flow in the ductus venosus, hepatic artery, or across the tricuspid valve, and on the basis of the results they are then classified as high-risk or low-risk groups.

Clinical Implementation of Cell-Free DNA Testing in Maternal Blood

The performance of screening for trisomies 21, 18, and 13 by cfDNA analysis of maternal blood is superior to that of the combined test.[11] However, the test is expensive, and it is therefore unlikely that it would be used for routine screening of the whole population. We have suggested that the best model of screening is to offer cfDNA testing contingent on the results of first-line screening by the combined test.[7,49] On the basis of the combined test, the population is divided into a very high-risk group, an intermediate-risk group, and a low-risk group. In this model, it is proposed that firstly, invasive testing is carried out in all cases in the very high-risk group, and secondly, cfDNA testing is carried out in the intermediate-risk group followed by invasive testing for those with a screen positive result (Fig. 8.7).

Such strategy would retain the advantages of the first trimester scan in the diagnosis of major defects and assessment of risk for pregnancy complications and would detect about 98% of fetuses with trisomies 21, 18, and 13, at an overall invasive testing rate of less than 1%. The intermediate-risk group requiring cfDNA testing constitutes about 25% of the population. However, this proportion can be reduced to about 10%, without affecting the overall performance of screening, by a first-line method of screening that includes measurement of ductus venosus PIV, in addition to fetal NT, FHR, and serum-free β-hCG, PAPP-A, PLGF, and AFP.[49]

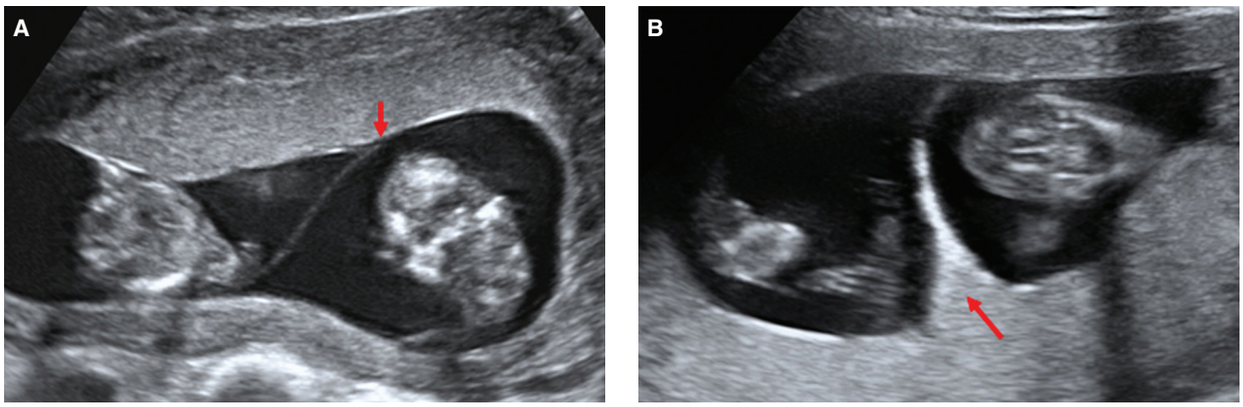

FIGURE 8.6: Ultrasound picture illustrating the difference in the junction of the intertwin membrane (shown by the *red arrow*) with the placenta in monochorionic **(A)** and dichorionic twins **(B)** at 12 weeks' gestation.

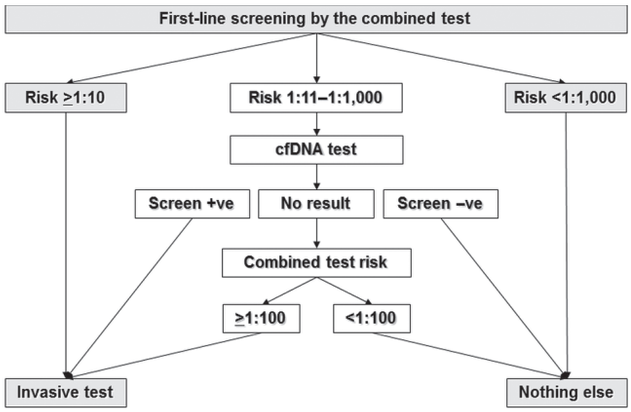

FIGURE 8.7: First-line screening by the combined test is carried out in all pregnancies. In those with a risk for trisomies 21, 18, or 13 ≥1:10, invasive testing is performed, and in those with a risk <1:1,000, there is no further testing. In women with risk between 1:11 and 1:1,000 cell-free (cf) DNA testing is carried out. In those with a positive cfDNA result, invasive testing is performed, and in those with a negative result, there is no further testing. In the group of women with no result from cfDNA testing, the results of the combined test are considered, and invasive testing is carried out for those with a risk for trisomy 21, 18, or 13 ≥1:100.

DIAGNOSIS OF MAJOR FETAL DEFECTS

The 11 to 13 weeks scan evolved over the last 20 years from essentially a scan for the measurement of fetal NT and CRL to one that includes a basic checklist for examination of the fetal anatomy with the intention of diagnosing major abnormalities, which are either lethal or associated with severe handicap, so that the parents can have the option of earlier and safer pregnancy termination.

Major fetal abnormalities fall into essentially three groups in relation to whether they can be detected at the 11 to 13 weeks scan.[50] Firstly, relatively easily detectable abnormalities, including body stalk anomaly, anencephaly, alobar holoprosencephaly, omphalocele, gastroschisis, and megacystis. The second category is anomalies not detectable in the first trimester, because they manifest only during the second or third trimester of pregnancy, including microcephaly, agenesis of the corpus callosum, semilobar holoprosencephaly, hypoplasia of the cerebellum or vermis, congenital pulmonary airway malformation, and bowel obstruction. A third group includes abnormalities that are potentially detectable in the first trimester, but whose diagnosis is significantly dependent on the objectives set for such a scan and consequently the time allocated for the fetal examination, the expertise of the sonographer, the quality of the equipment used and maternal body habitus, and secondly, the presence of an easily detectable marker for an underlying abnormality. A good example of such a marker in the first trimester is high NT that is found in some fetuses with lethal skeletal dysplasias, diaphragmatic hernia, and major cardiac defects.

Several studies reported the diagnosis of a wide range of fetal abnormalities during the first trimester scan. A randomized study of 35,792 pregnancies where a routine anomaly scan was carried out at 12 or 18 weeks using a checklist (skull, neck and brain, face, chest, heart, diaphragm, abdominal wall, stomach, kidneys, bladder, spine, and limbs), reported that the rate of prenatal detection of major abnormalities was not significantly different between the two groups (38% vs. 47%).[51] In our center, we conducted a prospective study on first trimester screening for aneuploidies that included a basic examination of the fetal anatomy in 45,191 pregnancies; the findings were compared with those at 20 to 23 weeks and with the postnatal examination.[50] Chromosomally abnormal cases were excluded from the analysis. Fetal abnormalities were observed in 488 (1.1%) cases and 213 (43.6%) of these were detected at 11 to 13 weeks. The early scan detected all cases of acrania, alobar holoprosencephaly, exomphalos, gastroschisis, megacystis, and body stalk anomaly, 77% of absent hand or foot, 50% of diaphragmatic hernia, 50% of lethal skeletal dysplasias, 60% of polydactyly, 34% of major cardiac defects, 5% of facial clefts, and 14% of open neural tube defects.

Suggested Protocol for First Trimester Anomaly Scan

The ultrasound examination can be performed transabdominally, using 3 to 7.5 MHz curvilinear transducers, but in about 1% of cases when there are technical difficulties to obtain adequate views, a transvaginal scan (3 to 9 MHz) should also be carried out. The time allocated for the ultrasound examination of the fetus should be about 20 minutes. It should be aimed to obtain a transverse section of the head to demonstrate the skull, midline echo, and the choroid plexuses, a midsagittal view of the face to demonstrate the nasal bone, sagittal section of the spine to demonstrate kyphoscoliosis, a transverse section of the thorax to demonstrate the four-chamber view of the heart and record blood flow across the tricuspid valve, transverse and sagittal sections of the trunk, and extremities to demonstrate the stomach, bladder, and abdominal insertion of the umbilical cord, all the long bones, hands, and feet.

Acrania and Anencephaly

The ossification of the skull and the development of the two cerebral hemispheres are usually evident at 11 weeks. In the absence of the cranial vault (acrania), the hemispheres of the brain are still recognizable. Subsequently, there is degeneration of the brain leading to exencephaly and later anencephaly. The diagnosis of anencephaly during the second trimester of pregnancy is based on the demonstration of absent cranial vault and cerebral hemispheres. In 11 to 13 weeks scan, the pathognomonic feature of anencephaly is acrania with the brain appearing either normal or at varying degrees of distortion and disruption (Fig. 8.8).[52]

Holoprosencephaly

Holoprosencephaly, with a birth prevalence of about 1 in 10,000, is characterized by a spectrum of cerebral abnormalities resulting from incomplete cleavage of the forebrain. At 11 weeks, it is already possible to clearly visualize falx cerebri and the butterfly appearance of the cerebral hemispheres, mainly represented by the two bulky choroid plexus of the lateral ventricles (Fig. 8.9). In the standard transverse view of the fetal head, alobar and semilobar holoprosencephaly are characterized by a single

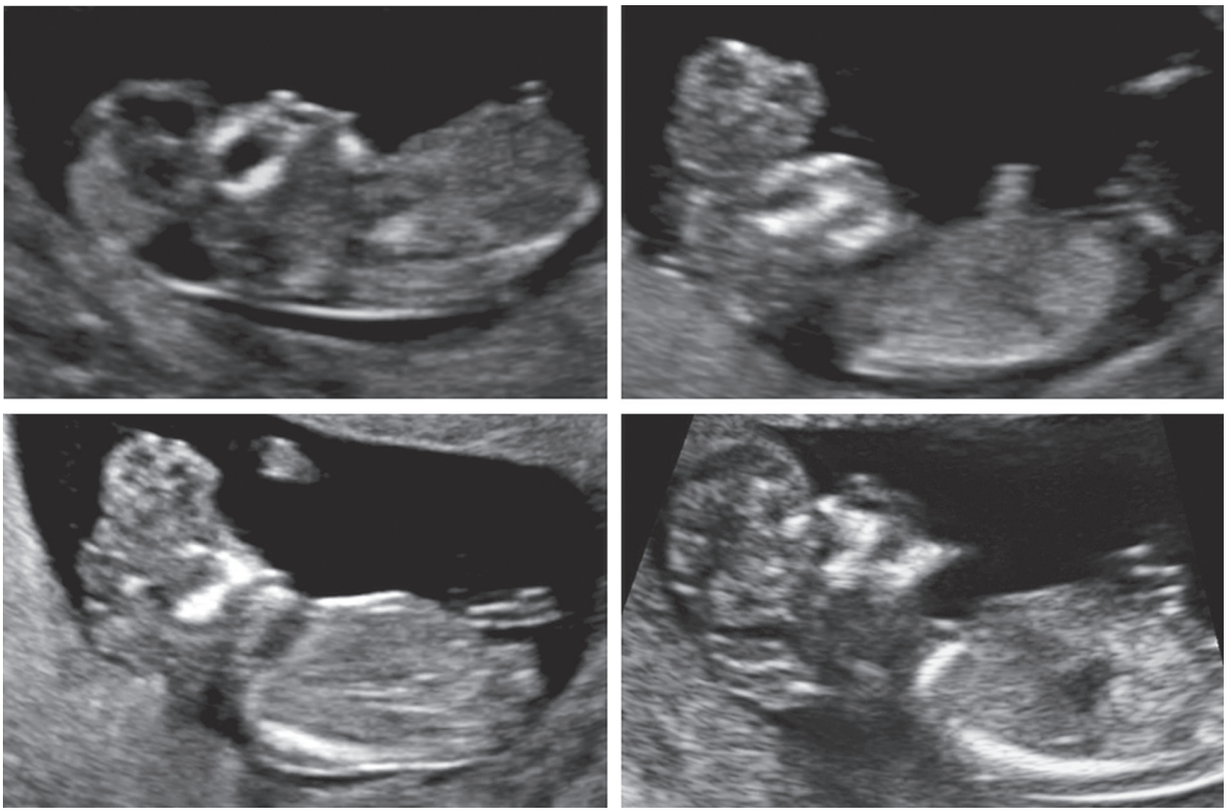

FIGURE 8.8: Acrania with varying degrees of distortion and disruption of the brain at 11 to 13 weeks' gestation.

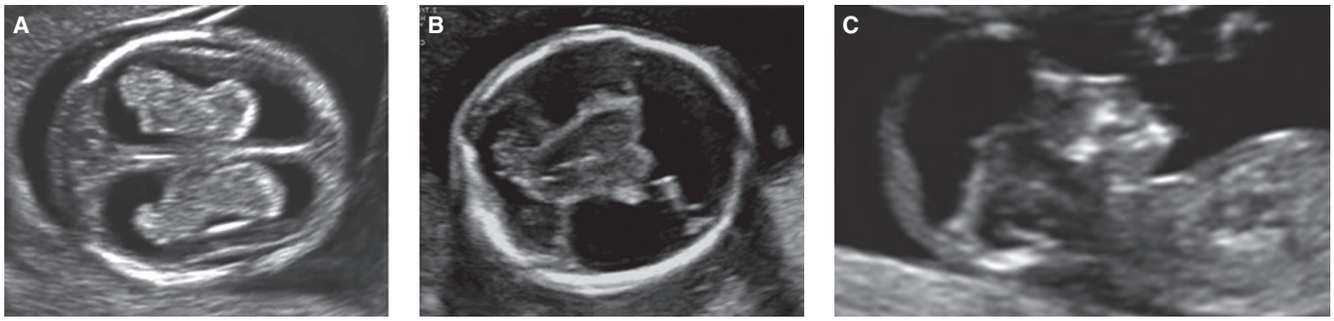

FIGURE 8.9: Cross-sectional view of the fetal brain at 12 weeks demonstrating the normal butterfly appearance of the lateral ventricles with the choroid plexuses **(A)** and alobar holoprosencephaly with fusion of the anterior horns of the lateral ventricles **(B)**. **C:** Sagittal view of the fetal brain demonstrating alobar holoprosencephaly.

dilated midline ventricle replacing the two lateral ventricles (fusion of the anterior horns of the lateral ventricles) or partial segmentation of the ventricles and the absence of the butterfly sign.[53] The alobar and semilobar types are often associated with facial defects, such as hypotelorism or cyclopia, facial cleft, and nasal hypoplasia or proboscis. In about 65% of cases diagnosed in the first trimester, there is an underlying aneuploidy, mainly trisomy 13.[54]

Open Neural Tube Defects

In almost all cases of open neural tube defects, there is an associated Arnold–Chiari malformation. In the second trimester of pregnancy, the manifestations of the Arnold–Chiari malformation are the lemon and banana signs by ultrasound.[55]

It has recently been realized that in open neural tube defects caudal displacement of the brain can be apparent at 11 to 13 weeks in the same midsagittal view of the fetal face as for measurement of fetal NT and assessment of the nasal bone.[56,57] In this view, the lower part of the fetal brain between the sphenoid bone anteriorly and the occipital bone posteriorly can be divided into the brain stem in the front and a combination of the fourth ventricle and cistern magna in the back (Fig. 8.10). In fetuses with open neural tube defects, the brain stem diameter is increased and the diameter of the fourth ventricle–cisterna magna complex is decreased.

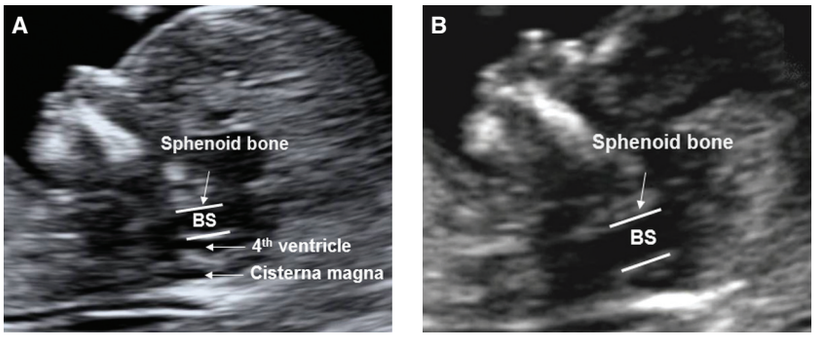

FIGURE 8.10: Midsagittal view of the fetal brain in a normal **(A)** and a spina bifida **(B)** fetus at 12 weeks demonstrating the measurement of brain stem *(BS)* diameter. In open spina bifida, the brain stem diameter is increased.

Major Cardiac Defects

Abnormalities of the heart and great arteries are the most common congenital defects and they account for about 20% of all stillbirths and 30% of neonatal deaths because of congenital defects.[58] Although most major cardiac defects are amenable to prenatal diagnosis by specialist fetal echocardiography, routine ultrasound screening in pregnancy fails to identify the majority of affected fetuses.[59–61] Consequently, effective population-based prenatal diagnosis necessitates improved methods of identifying the high-risk group for referral to specialists.

The traditional method of screening for cardiac defects, which relies on family history of cardiac defects, maternal history of diabetes mellitus, and maternal exposure to teratogens, identifies only about 10% of affected fetuses.[62]

A major improvement in screening for cardiac defects came with the realization that the risk for cardiac defects increases with fetal NT thickness and is also increased in those with abnormal flow in the ductus venosus and across the tricuspid valve.[22,24,36,63–66] Reversed a-wave in the ductus venosus or tricuspid regurgitation, observed in about 2% and 1%, respectively of normal fetuses, is found in 30% of affected fetuses. Specialist fetal echocardiography for cases with NT above the 99th centile and those with reversed a-wave in the ductus venosus or tricuspid regurgitation, irrespective of NT, would require cardiac scanning in about 4% of the population and would detect about 50% of major cardiac defects.

Patients identified by first trimester screening as being at high risk for cardiac defects need not wait until 20 weeks for specialist echocardiography. First trimester fetal echocardiography is technically more difficult than at 20 weeks, because the heart is much smaller and the fetus is usually more mobile. However, it is still possible to demonstrate the four-chamber view, outflow tracts, arterial duct, and aortic arch (Fig. 8.11). The overall success rate in the assessment of the fetal heart is about 45% at 11 weeks and 90% at 13 weeks.[67] In many cases, a scan as early as at 13 weeks' gestation can effectively reassure the parents that there is no suggestion of a major cardiac defect. Similarly, in many cases with a major cardiac defect, the early scan can raise a suspicion that a defect is present, and often leads to the correct diagnosis even at this gestational age. However, an echocardiogram done later in gestation is still important, especially in those cases where the fetal heart appears to be normal during the early evaluation.

Diaphragmatic Hernia

This is a sporadic defect with a birth prevalence of about 1 in 4,000. In up to 30% of affected fetuses, there are associated chromosomal abnormalities, mainly trisomy 18, or other anomalies. Increased NT thickness is present in about 40% of fetuses with diaphragmatic hernia, including more than 80% of those that result in neonatal death owing to pulmonary hypoplasia and in about 20% of the survivors (Fig. 8.12).[68] It is possible that in fetuses with diaphragmatic hernia and increased NT, the intrathoracic herniation of the abdominal viscera occurs in the first trimester and prolonged compression of the lungs causes pulmonary hypoplasia. In the cases where diaphragmatic hernia is associated with a good prognosis, the intrathoracic herniation of viscera may be delayed until the second or third trimesters of pregnancy.

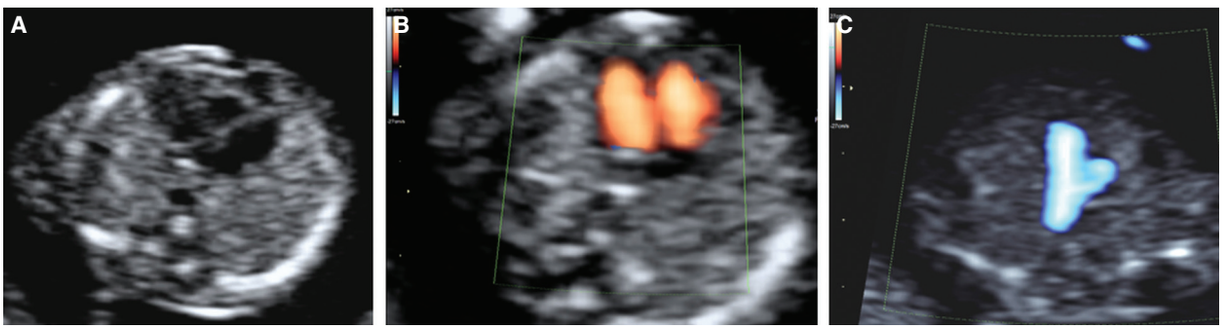

FIGURE 8.11: Four-chamber view of the fetal heart at 12 weeks' gestation **(A)**, color flow imaging of an apical four-chamber view demonstrating equal diastolic flows from right and left atrium into right and left ventricle **(B)**, and color flow imaging showing the V-sign formed by the ductal arch and aortic arch **(C)**.

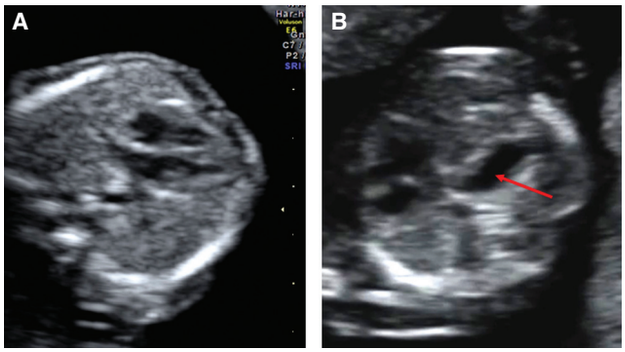

FIGURE 8.12: Cross-sectional view of the fetal thorax illustrating the normal position of the heart and lungs **(A)**, and intrathoracic herniation of the stomach (*arrow* in **B**) in a case of diaphragmatic hernia.

Ventral Wall Defects

Prenatal diagnosis of omphalocele by ultrasound is based on the demonstration of the midline anterior abdominal wall defect, the herniated sac with its visceral contents, and the umbilical cord insertion at the apex of the sac (Fig. 8.13). At 8 to 10 weeks of gestation, all fetuses demonstrate herniation of the midgut that is visualized as a hyperechogenic mass in the base of the umbilical cord. Retraction into the abdominal cavity is normally completed by 12 weeks. At 11 to 13 weeks, exomphalos is observed in about 1:1,000 fetuses, and in 55% of cases there is an associated chromosomal abnormality, usually trisomy 18.[54] Omphalocele containing liver is an irreversible anatomical defect, whereas exomphalos containing only bowel can be a transient abnormality. If the fetal karyotype is found to be normal, the condition is likely to resolve spontaneously.

Gastroschisis

This is a sporadic defect with a birth prevalence of about 1 in 4,000. It is rarely associated with chromosomal abnormalities. Evisceration of the intestine occurs through a small abdominal wall defect located just to the right of an intact umbilical cord, and the loops of intestine lie uncovered in the amniotic fluid (Fig. 8.14). The condition persists throughout pregnancy. Prenatal diagnosis by ultrasound is based on the demonstration of the normally situated umbilicus and the herniated loops of intestine, which are free floating.

Megacystis

The fetal bladder can be visualized by sonography in about 95% of fetuses at 11 weeks of gestation and in all cases by 13 weeks. At this gestation, the fetal bladder length is normally less than 7 mm. Fetal megacystis in the first trimester, defined by a longitudinal bladder diameter 7 mm or more, is found in about 1 in 1,500 pregnancies. The condition is associated with chromosomal defects, mainly trisomies 13 and 18, which are found in about 30% of fetuses (Fig. 8.15).[54,69,70] In chromosomally normal fetuses, mild megacystis usually resolves spontaneously, but in those with bladder diameter greater than 15 mm, there is progression to severe obstructive uropathy. The presence of smooth muscle in the bladder and autonomic innervation occur only after 13 weeks, and before this gestation the bladder wall consists of epithelium and connective tissue with no contractile elements. It is therefore likely that in the majority of fetuses with mild megacystis, there is no underlying urethral obstruction but a temporary malfunction of the bladder.

Skeletal Dysplasias

In the first trimester, it is possible to evaluate the presence of the three segments of the limbs (rhizomelic, mesomelic, and acromelic) and their movements and, therefore, to raise the suspicion of polydactyly, clenched hands, clubfoot, and some of the most severe dysplasias such as thanatophoric dysplasia, osteogenesis imperfecta, achondroplasia, achondrogenesis, and asphyxiating thoracic dystrophy. Many severe skeletal defects that can be diagnosed in the first trimester of pregnancy are usually associated with increased NT thickness. The cause of increased NT in some of the skeletal dysplasias may be venous congestion in the head and neck due to superior mediastinal compression by the narrow chest. An additional or alternative mechanism for the increased NT may be the altered composition of the extracellular matrix found in association with some of the skeletal dysplasias, such as osteogenesis imperfecta.

Body Stalk Anomaly

This lethal sporadic anomaly has a birth prevalence of 1 in 15,000. The ultrasound features include major abdominal wall defect, severe kyphoscoliosis, and short umbilical cord with a single artery.[71] Half of the fetal body is seen in the amniotic

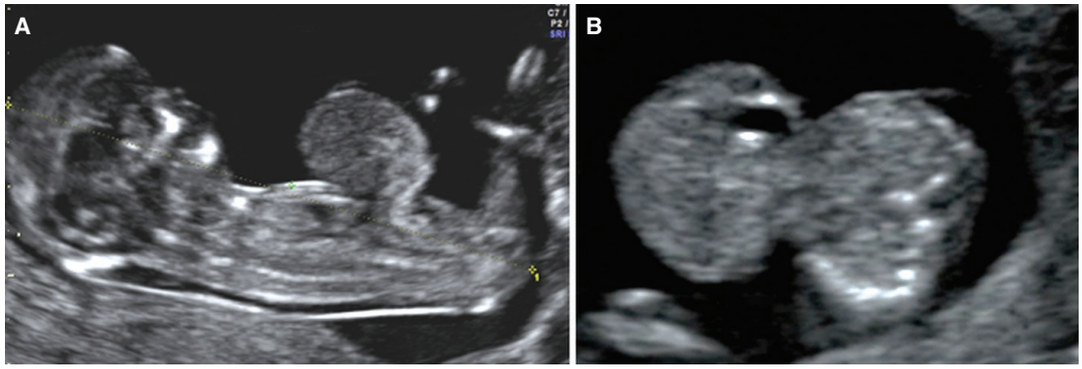

FIGURE 8.13: Sagittal **(A)** and transverse **(B)** views of the fetal abdomen at the level of the umbilicus illustrating cases of exomphalos containing liver at 12 weeks' gestation.

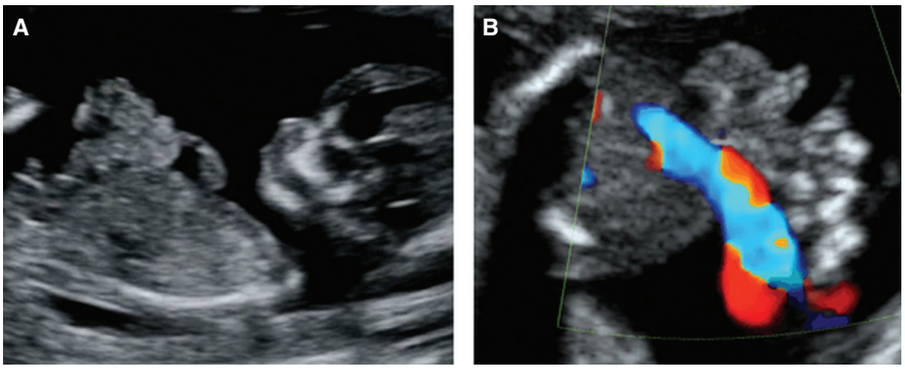

FIGURE 8.14: Sagittal **(A)** and transverse **(B)** views of the fetal abdomen at the level of the umbilicus illustrating cases of gastroschisis at 12 weeks' gestation.

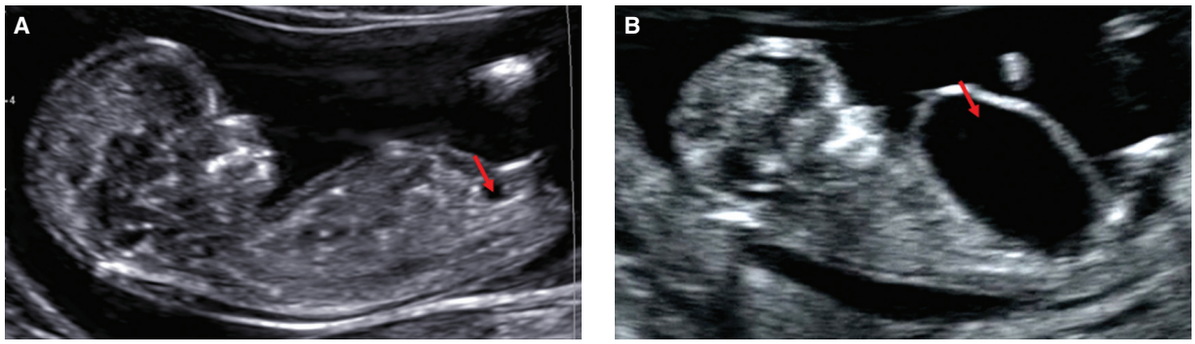

FIGURE 8.15: Midsagittal illustrating a normal bladder (*arrow*) in a fetus at 12 weeks gestation **(A)** and one with megacystis (*arrow*) **(B)**.

cavity and the other half in the celomic cavity, suggesting that early amnion rupture before obliteration of the celomic cavity is a possible cause of the syndrome (Fig. 8.16). A defect of somatic clefting is also a plausible contributing factor.[72] The fetal NT is increased in about 85% of the cases, but the karyotype is usually normal.

ASSESSMENT OF RISK FOR PREGNANCY COMPLICATIONS

The current approach to prenatal care, which involves office visits at 16, 24, 28, 30, 32, 34, and 36 weeks and then weekly until delivery, was established 80 years ago.[73,74] The high concentration of visits in the third trimester implies that, firstly, most complications occur at this late stage of pregnancy and, secondly, that most major adverse outcomes are unpredictable during the first or even the second trimester.

In the last 20 years, it has become apparent that an integrated first hospital visit at 11 to 13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests can define the patient-specific risk for a wide spectrum of pregnancy complications, including miscarriage and stillbirth, preeclampsia, preterm birth, gestational diabetes, fetal growth restriction, and macrosomia.[75] Early estimation of patient-specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a

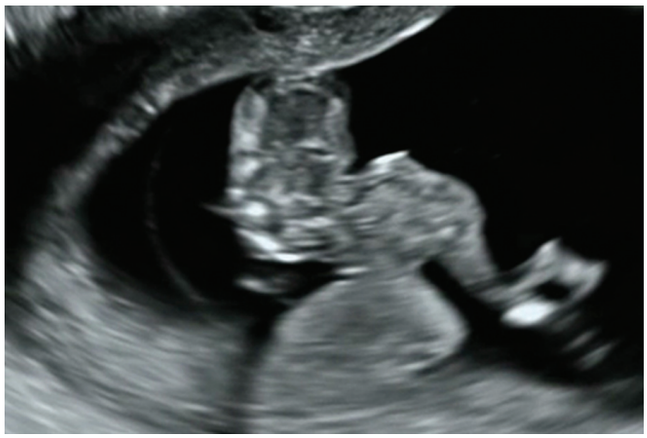

FIGURE 8.16: Fetus with body stalk anomaly at 12 weeks' gestation.

series of routine visits to a more individualized patient- and disease-specific approach in terms of both the schedule and the content of such visits. Each visit would have a predefined objective, and the findings will generate likelihood ratios that can be used to estimate the individual patient- and disease-specific estimated risk from the initial assessment at 11 to 13 weeks.

At 11 to 13 weeks, the great majority of women would be classified as being at low risk for pregnancy complications, and a small proportion of women would be selected as being at high

risk (see Fig. 8.2). In the low-risk group, the number of routine indicated medical visits could potentially be reduced to as low as three. A subsequent visit at 20 to 22 weeks would reevaluate fetal anatomy and growth and reassess risk for such complications as preeclampsia and preterm delivery. Another visit during the third trimester will assess maternal and fetal well-being and determine the best time and method of delivery. The high-risk group can have close surveillance in specialist clinics in terms of both the investigations to be performed and the personnel involved in the provision of care. In each of these visits, their risk will be reassessed and they will either remain high-risk status or they will revert to low-risk status, in which case the intensity of their care can be reduced.

Future research will inevitably expand the number of conditions that can be identified in early pregnancy and define genetic markers of disease that will improve the accuracy of the a priori risk based on maternal characteristics and medical history. Similarly, new biophysical and biochemical markers will be described that may replace some of the current ones and modify the value of others. With the passage of time, it will become necessary to reevaluate and improve the timing and content of each visit and the likelihood ratios for each test. Early identification of high-risk groups will also stimulate further research that will define the best protocol for their follow-up and development of strategies for the prevention of disorders of pregnancy or mitigation of their adverse consequences. It is likely that the new challenge for improvement of pregnancy outcome will be met by inverting the pyramid of antenatal care (Fig. 8.17) to introduce on a large scale and in a systematic fashion a new model of antenatal care that will be based on the results of a comprehensive assessment at 11 to 13 weeks.[75]

Preterm Birth

Preterm birth is the leading cause of perinatal death and handicap in children, and the vast majority of mortality and morbidity relates to early delivery before 34 weeks, which occurs in about 2% of singleton pregnancies. In two-thirds of the cases, this is due to spontaneous onset of labor or preterm prelabor rupture of membranes, and in the other one-third, it is iatrogenic, mainly because of preeclampsia.[76]

The patient-specific risk for spontaneous delivery before 34 weeks can be determined at 11 to 13 weeks by an algorithm combining maternal characteristics and obstetric history with the sonographic measurement of cervical length.[77,78] In the measurement of cervical length, it is important to distinguish between the true cervix, characterized by the presence of the endocervical canal, which is bordered by the endocervical mucosa, which is usually of decreased echogenicity compared with the surrounding tissues, and the isthmus (Fig. 8.18).

Effective early identification of the high-risk group for subsequent spontaneous early delivery could potentially improve outcome by directing such patients to specialist clinics for regular monitoring of cervical length, and stimulating research for identification of potentially useful biomarkers and the investigation of the potential role of earlier intervention with such measures as prophylactic use of progesterone or cervical cerclage.

Preeclampsia

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences are inversely related to the gestational age at onset of the disease. Consequently, in screening for preeclampsia, the condition should be subdivided according to gestational age at delivery.

Algorithms that combine maternal characteristics, mean arterial pressure, uterine artery PI, and maternal serum biochemical tests at 11 to 13 weeks could potentially identify about 90%, 80%, and 60% of pregnancies that subsequently develop early (before 34 weeks), intermediate (34 to 37 weeks), and late (after 37 weeks) preeclampsia, for a FPR of 5%.[79,80] Further investigations will determine whether in the high-risk group pharmacological interventions, such as low-dose aspirin, starting from the first trimester could improve placentation and reduce the prevalence of the disease.[81,82]

In the measurement of the uterine artery pulsatility index (PI) at 11 to 13 weeks' gestation, a sagittal section of the uterus should be obtained, and the cervical canal and internal cervical os identified. The transducer should be gently tilted from side to side, and color flow mapping should be used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os (Fig. 8.19). Pulsed wave Doppler should be used with the sampling gate set at 2 mm to cover the whole vessel, and care should be taken to ensure that the angle of insonation is less than 30° When three similar consecutive waveforms are obtained, the uterine artery PI should be measured and the mean PI of the left and right arteries calculated.

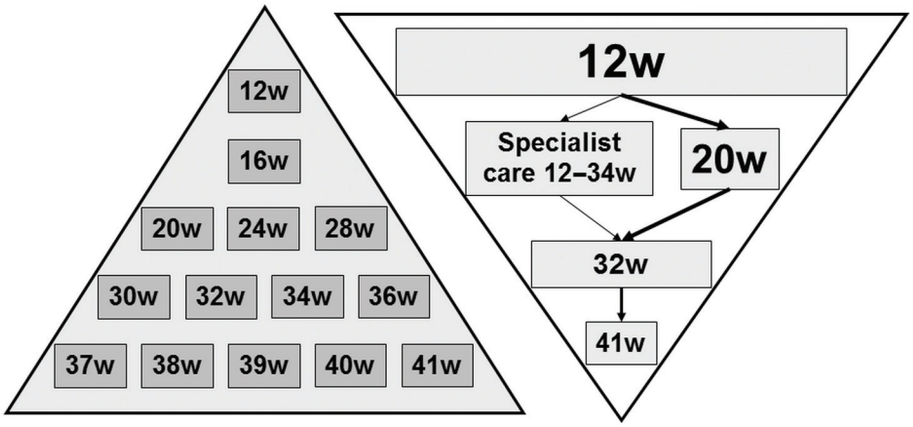

FIGURE 8.17: Pyramid of gestational ages according to the traditional model of prenatal care established in the 1920s **(left)** and according to the proposed new model of inverted pyramid **(right)**.

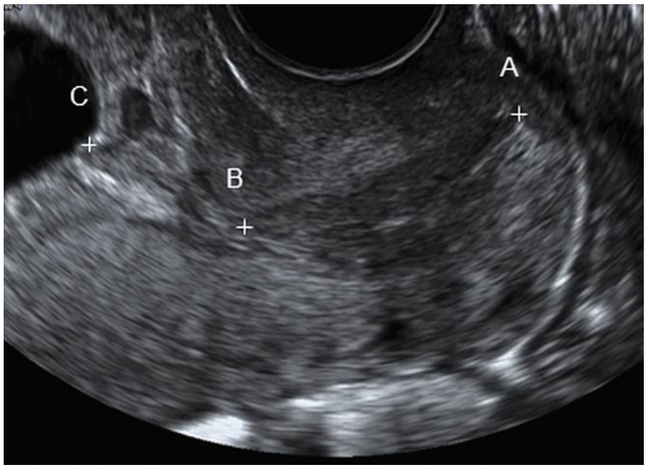

FIGURE 8.18: Ultrasound picture illustrating the measurement of the length of the endocervix (*A* to *B*) and the isthmus (*B* to *C*).

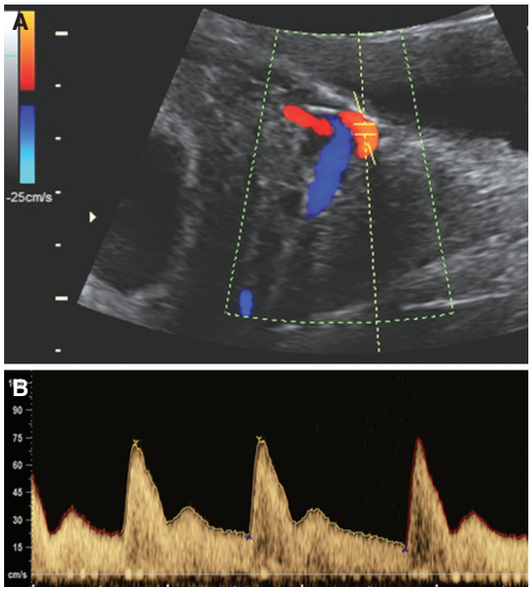

FIGURE 8.19: Parasagittal view of the cervix with color flow imaging to illustrate the uterine arteries **(A)** and characteristic waveform at 12 weeks' gestation **(B)**.

In conclusion, the first trimester scan has evolved recently into one of the milestones of prenatal care. As shown in this chapter, the aims of the 11 to 13+6 weeks scan include not only the confirmation of the viability of the pregnancy and the accurate dating of the gestation based on the CRL measurement but, especially screening for aneuploidies and various pregnancy's complications, early diagnosis of major fetal abnormalities, and the detection of multiple pregnancies with reliable identification of chorionicity.

REFERENCES

1. Tabor A, Alfirevic Z. Update on procedure-related risks for prenatal diagnosis techniques. *Fetal Diagn Ther*. 2010;27:1–7.
2. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. *Prenat Diagn*. 2011;31:7–15.
3. Snijders RJM, Holzgreve W, Cuckle H, et al. Maternal age-specific risks for trisomies at 9–14 weeks' gestation. *Prenat Diagn*. 1994;14:543–552.
4. Snijders RJM, Sebire NJ, Nicolaides KH. Maternal age and gestational age-specific risks for chromosomal defects. *Fetal Diagn Ther*. 1995;10:356–367.
5. Kagan KO, Wright D, Valencia C, et al. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free beta-hCG and pregnancy-associated plasma protein-A. *Hum Reprod*. 2008;23:1968–1975.
6. Wright D, Syngelaki A, Bradbury I, et al. First trimester screening for trisomies 21, 18 and 13 by ultrasound and biochemical testing. *Fetal Diagn Ther*. 2014;35(2):118–126.
7. Syngelaki A, Pergament E, Homfray T, et al. Replacing the combined test by cell-free DNA testing in screening for trisomies 21, 18 and 13: impact on the diagnosis of other aneuploidies. *Fetal Diagn Ther*. 2014;Feb 8. [Epub ahead of print]
8. Kagan KO, Anderson JM, Anwandter G, et al. Screening for triploidy by the risk algorithms for trisomies 21, 18 and 13 at 11 weeks to 13 weeks and 6 days of gestation. *Prenat Diagn*. 2008;28:1209–1213.
9. Sebire NJ, Snijders RJ, Brown R, et al. Detection of sex chromosome abnormalities by nuchal translucency screening at 10–14 weeks. *Prenat Diagn*. 1998;18:581–584.
10. Spencer K, Tul N, Nicolaides KH. Maternal serum free beta-hCG and PAPP-A in fetal sex chromosome defects in the first trimester. *Prenat Diagn*. 2000;20:390–394.
11. Gil MM, Akolekar R, Quezada MS, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta analysis. *Fetal Diagn Ther*. 2014;Feb 8. [Epub ahead of print]
12. Nicolaides KH, Syngelaki A, Gil MM, et al. Prenatal diagnosis of triploidy from cell-free DNA testing in maternal blood. *Fetal Diagn Ther*. 2013;Oct 10. [Epub ahead of print]
13. Guex N, Iseli C, Syngelaki A, et al. A robust 2nd generation genome-wide test for fetal aneuploidy based on shotgun sequencing cell-free DNA in maternal blood. *Prenat Diagn*. 2013;33:707–710.
14. Srinivasan A, Bianchi DW, Huang H, et al. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. *Am J Hum Genet*. 2013;92:167–176.
15. Nicolaides KH, Azar G, Byrne D, et al. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ*. 1992;304:867–889.
16. Molina FS, Avgidou K, Kagan KO, et al. Cystic hygromas, nuchal edema, and nuchal translucency at 11–14 weeks of gestation. *Obstet Gynecol*. 2006; 107:678–683.
17. Snijders RJ, Noble P, Sebire N, et al; Fetal Medicine Foundation First Trimester Screening Group. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation. *Lancet*. 1998;352:343–346.
18. Wald NJ, Rodeck C, Hackshaw AK, et al; SURUSS Research Group. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *Health Technol Assess*. 2003;7:1–88.
19. Malone FD, Canick JA, Ball RH, et al; for the First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med*. 2005;353: 2001–2011.
20. Souka AP, Snidjers RJM, Novakov A, et al. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 1998;11:391–400.
21. Souka AP, Von Kaisenberg CS, Hyett JA, et al. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol*. 2005;192:1005–1021.
22. Hyett J, Perdu M, Sharland G, et al. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *BMJ*. 1999;318:81–85.
23. Hyett J, Moscoso G, Papapanagiotou G, et al. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol*. 1996;7:245–250.
24. Atzei A, Gajewska K, Huggon IC, et al. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol*. 2005;26:154–157.
25. Cicero S, Curcio P, Papageorghiou A, et al. Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks of gestation: an observational study. *Lancet*. 2001; 358:1665–1667.
26. Cicero S, Avgidou K, Rembouskos G, et al. Nasal bone in first-trimester screening for trisomy 21. *Am J Obstet Gynecol*. 2006;195:109–114.
27. Kagan KO, Cicero S, Staboulidou I, et al. Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol*. 2009;33:259–264.
28. Matias A, Gomes C, Flack N, et al. Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow. *Ultrasound Obstet Gynecol*. 1998;12:380–384.
29. Maiz N, Valencia C, Kagan KO, et al. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. *Ultrasound Obstet Gynecol*. 2009;33:512–517.
30. Huggon IC, DeFigueiredo DB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11–14 weeks of gestation. *Heart*. 2003;89:1071–1073.

31. Faiola S, Tsoi E, Huggon IC, et al. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan. *Ultrasound Obstet Gynecol*. 2005;26:22–27.
32. Kagan KO, Valencia C, Livanos P, et al. Tricuspid regurgitation in screening for trisomies 21, 18 and 13 and Turner syndrome at 11+0 to 13+6 weeks of gestation. *Ultrasound Obstet Gynecol*. 2009;33:18–22.
33. Bilardo CM, Timmerman E, Robles de Medina PG, et al. Low-resistance hepatic artery flow in first trimester fetuses: an ominous sign. *Ultrasound Obstet Gynecol*. 2011;37(4):438–43. doi:10.1002/uog.7766.
34. Zvanca M, Gielchinsky Y, Abdeljawad F, et al. Hepatic artery Doppler in trisomy 21 and euploid fetuses at 11–13 weeks. *Prenat Diagn*. 2011;31:22–27.
35. Maiz N, Nicolaides KH. Ductus venosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. *Fetal Diagn Ther*. 2010;28:65–71.
36. Matias A, Huggon I, Areias JC, et al. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10–14 weeks. *Ultrasound Obstet Gynecol*. 1999;14:307–310.
37. Maiz N, Kagan KO, Milovanovic Z, et al. Learning curve for Doppler assessment of ductus venosus flow at 11 + 0 to 13 + 6 weeks. *Ultrasound Obstet Gynecol*. 2008;31:503–506.
38. Maiz N, Valencia C, Emmanuel EE, et al. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11–13 + 6 weeks of gestation. *Obstet Gynecol*. 2008;112:598–605.
39. Borrell A, Borobio V, Bestwick JP, et al. Ductus venosus pulsatility index as an antenatal screening marker for Down's syndrome: use with the Combined and Integrated tests. *J Med Screen*. 2009;16:112–118.
40. Maiz N, Wright D, Ferreira AF, et al. A mixture model of ductus venosus pulsatility index in screening for aneuploidies at 11–13 weeks' gestation. *Fetal Diagn Ther*. 2012;31:221–229.
41. Falcon O, Faiola S, Huggon I, et al. Fetal tricuspid regurgitation at the 11 + 0 to 13 + 6-week scan: association with chromosomal defects and reproducibility of the method. *Ultrasound Obstet Gynecol*. 2006;27:609–612.
42. Nicolaides KH, Spencer K, Avgidou K, et al. Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. *Ultrasound Obstet Gynecol*. 2005;25:221–226.
43. Sepulveda W, Sebire NJ, Hughes K, et al. The lambda sign at 10–14 weeks of gestation as a predictor of chorionicity in twin pregnancies. *Ultrasound Obstet Gynecol*. 1996;7:421–423.
44. Sebire NJ, Snijders RJ, Hughes K, et al. Screening for trisomy 21 in twin pregnancies by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Br J Obstet Gynaecol*. 1996;103:999–1003.
45. Vandecruys H, Faiola S, Auer M, et al. Screening for trisomy 21 in monochorionic twins by measurement of fetal nuchal translucency thickness. *Ultrasound Obstet Gynecol*. 2005;25:551–553.
46. Spencer K, Nicolaides KH. First trimester prenatal diagnosis of trisomy 21 in discordant twins using fetal nuchal translucency thickness and maternal serum free beta-hCG and PAPP-A. *Prenat Diagn*. 2000;20:683–684.
47. Spencer K, Nicolaides KH. Screening for trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years experience. *BJOG*. 2003;110:276–280.
48. Madsen H, Ball S, Wright D, et al. A re-assessment of biochemical marker distributions in T21 affected and unaffected twin pregnancies in the first trimester. *Ultrasound Obstet Gynecol*. 2011;37:38–47.
49. Nicolaides KH, Syngelaki A, Poon LC, et al. First-trimester contingent screening for trisomies 21, 18 and 13 by biomarkers and maternal blood cell-free DNA testing. *Fetal Diagn Ther*. 2013;Oct 26. [Epub ahead of print]
50. Syngelaki A, Chelemen T, Dagklis T, et al. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. *Prenat Diagn*. 2011;31:90–102.
51. Saltvedt S, Almström H, Kublickas M, et al. Detection of malformations in chromosomally normal fetuses by routine ultrasound at 12 or 18 weeks of gestation—a randomised controlled trial in 39,572 pregnancies. *BJOG*. 2006;113:664–674.
52. Johnson SP, Sebire NJ, Snijders RJM, et al. Ultrasound screening for anencephaly at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 1997;9:14–16.
53. Sepulveda W, Dezerega V, Be C. First-trimester sonographic diagnosis of holoprosencephaly: value of the "butterfly" sign. *J Ultrasound Med*. 2004;23:761–765.
54. Kagan KO, Stamboulidou I, Syngelaki A, et al. The 11–13-week scan: diagnosis and outcome of holoprosencephaly, exomphalos and megacystis. *Ultrasound Obstet Gynecol*. 2010;36:10–14.
55. Nicolaides KH, Campbell S, Gabbe SG, et al. Ultrasound screening for spina bifida: cranial and cerebellar signs. *Lancet*. 1986;2:72–74.
56. Chaoui R, Benoit B, Mitkowska-Wozniak H, et al. Assessment of intracranial translucency (IT) in the detection of spina bifida at the 11–13-week scan. *Ultrasound Obstet Gynecol*. 2009;34:249–252.
57. Lachmann R, Chaoui R, Moratalla J, et al. Posterior brain in fetuses with spina bifida at 11–13 weeks. *Prenat Diagn*. 2011;31:103–106.
58. Office for National Statistics. *Mortality Statistics, Childhood, Infancy and Perinatal*. Newport, England: Office for National Statistics; 2007. Series DH3, 40.
59. Bull C. Current and potential impact of fetal diagnosis on prevalence and spectrum of serious congenital heart disease at term in the UK. *Lancet*. 1999;35:1242–1247.
60. Bricker L, Garcia J, Henderson J, et al. Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views. *Health Technol Assess*. 2000;4:1–193.
61. Tegnander E, Williams W, Johansen OJ, et al. Prenatal detection of heart defects in a non-selected population of 30,149 fetuses-detection rates and outcome. *Ultrasound Obstet Gynecol*. 2006;27:252–265.
62. Allan LD. Echocardiographic detection of congenital heart disease in the fetus: present and future. *Br Heart J*. 1995;74:103–106.
63. Maiz N, Plasencia W, Dagklis T, et al. Ductus venosus Doppler in fetuses with cardiac defects and increased nuchal translucency thickness. *Ultrasound Obstet Gynecol*. 2008;31:256–260.
64. Martinez JM, Comas M, Borrell A, et al. Abnormal first-trimester ductus venosus blood flow: a marker of cardiac defects in foetuses with normal karyotype and nuchal translucency. *Ultrasound Obstet Gynecol*. 2010;35:267–272.
65. Chelemen T, Syngelaki A, Maiz M, et al. Contribution of ductus venosus Doppler in first trimester screening for major cardiac defects. *Fetal Diagn Ther*. 2011;29:127–134.
66. Pereira S, Ganapathy R, Syngelaki A, et al. Contribution of fetal tricuspid regurgitation in first trimester screening for major cardiac defects. *Obstet Gynecol*. 2011;117:1384–1391.
67. Persico N, Moratalla J, Lombardi CM, et al. Fetal echocardiography at 11–13 weeks by transabdominal high frequency ultrasound. *Ultrasound Obstet Gynecol*. 2011;37:296–301.
68. Sebire NJ, Snijders RJM, Davenport M, et al. Fetal nuchal translucency thickness at 10–14 weeks of gestation and congenital diaphragmatic hernia. *Obstet Gynecol*. 1997;90:943–947.
69. Sebire NJ, von Kaisenberg C, Rubio C, et al. Fetal megacystis at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 1996;8:387–390.
70. Liao AW, Sebire NJ, Geerts L, et al. Megacystis at 10–14 weeks of gestation: chromosomal defects and outcome according to bladder length. *Ultrasound Obstet Gynecol*. 2003;21:338–341.
71. Daskalakis G, Sebire NJ, Jurkovic D, et al. Body stalk anomaly at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol*. 1997;10:416–418.
72. Paul C, Zosmer N, Jurkovic D, et al. A case of body stalk anomaly at 10 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001;17:157–159.
73. Ballantyne JW. A plea for a pro-maternity hospital. *BMJ*. 1901;2101:813–814.
74. Ministry of Health Report. *1929 Memorandum on Antenatal Clinics: Their Conduct and Scope*. London, England: His Majesty's Stationery Office; 1930.
75. Nicolaides KH. Turning the pyramid of prenatal care. *Fetal Diagn Ther*. 2011;29:183–196.
76. Celik E, To M, Gajewska K, et al; for the Fetal Medicine Foundation Second Trimester Screening Group. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. *Ultrasound Obstet Gynecol*. 2008;31:549–554.
77. Beta J, Ventura W, Akolekar R, et al. Prediction of spontaneous preterm delivery from maternal factors and placental perfusion and function at 11–13 weeks. *Prenat Diagn*. 2011;31:75–83.
78. Greco E, Lange A, Ushakov F, et al. Prediction of spontaneous preterm delivery from endocervical length at 11–13 weeks. *Prenat Diagn*. 2011;31:84–89.
79. Akolekar R, Syngelaki A, Sarquis R, et al. Prediction of preeclampsia from biophysical and biochemical markers at 11–13 weeks. *Prenat Diagn*. 2011;31:66–74.
80. Akolekar R, Syngelaki A, Poon L, et al. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013;33:8–15.
81. Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol*. 2010;116:402–414.
82. Roberge S, Villa P, Nicolaides K, et al. Early administration of low dose aspirin for the prevention of preterm and term pre-eclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther*. 2012;31:141–146.