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Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks

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Objective To examine the performance of the 11–13 weeks scan in detecting non-chromosomal abnormalities.

Methods Prospective first-trimester screening study for aneuploidies, including basic examination of the fetal anatomy, in 45 191 pregnancies. Findings were compared to those at 20–23 weeks and postnatal examination.

Results Aneuploidies ($n = 332$) were excluded from the analysis. Fetal abnormalities were observed in 488 (1.1%) of the remaining 44 859 cases; 213 (43.6%) of these were detected at 11–13 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 *spina bifida*, but none of agenesis of the corpus callosum, cerebellar or vermian hypoplasia, echogenic lung lesions, bowel obstruction, most renal defects or talipes. Nuchal translucency (NT) was above the 95th percentile in 34% of fetuses with major cardiac defects.

Conclusion At 11–13 weeks some abnormalities are always detectable, some can never be and others are potentially detectable depending on their association with increased NT, the phenotypic expression of the abnormality with gestation and the objectives set for such a scan.

Supporting information may be found in the online version of this article.

KEY WORDS: first-trimester screening; fetal abnormalities; nuchal translucency; ultrasound; prenatal diagnosis

INTRODUCTION

In the United Kingdom, the National Institute for Clinical Excellence (NICE) has issued guidelines on routine prenatal care recommending that pregnant women should be offered two ultrasound scans in pregnancy (National Collaborating Centre for Women's and Children's Health, 2008). The primary aims of the first scan at 11–13 weeks are to establish gestational age from the measurement of fetal crown–rump length (CRL), detect multiple pregnancies and determine chorionicity and to measure fetal nuchal translucency (NT) thickness as part of combined screening for trisomy 21. The primary aim of the second scan, which is carried out at about 20 weeks, is the detection of structural fetal abnormalities.

A systematic review of studies in the 1990s on the clinical effectiveness of the routine second-trimester scan reported that the overall prevalence of fetal abnormalities was 2% and about 45% of these were detected (Bricker *et al*., 2000). However, there were large differences between studies in detection rates which ranged from 15 to 85% and this variation can be attributed to differences in the abnormalities included in their analysis, the rate and method of follow-up of the screened population and the protocols followed for examination of the fetus. There were also large differences in overall detection rates according to the type of fetal anomaly, being 97% for anencephaly, 67% for *spina bifida*, 33% for facial cleft, 56% for univentricular heart, 45% for atrio-ventricular septal defect and 2% for atrial or ventricular septal defects, 45% for diaphragmatic hernia, 100% for exomphalos and gastroschisis, 67% for urogenital abnormalities and 24% for skeletal defects. The rates of detection for some of these abnormalities are similar to those of a recent report from the European Network for Surveillance of Congenital Anomalies, which includes data from registries in 20 countries and covers 28% of all births in the European Union (Garne *et al*., 2010). During 2003–2007, the prevalence of all major non-chromosomal abnormalities was 2% and the prenatal detection rates for anencephaly, *spina bifida*, hypoplastic left heart and gastroschisis were 96, 68, 65 and 83%, respectively.

Several studies on the first-trimester scan reported the diagnosis of a wide range of fetal abnormalities,

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but in most studies the abnormalities were either a coincidental finding during screening for aneuploidies or they were detected after detailed examination of euploid fetuses because of increased NT (Souka *et al*., 2005). In this respect, the findings of reported studies do not reflect the true performance of the 11–13 weeks scan in screening for non-chromosomal abnormalities. The only exception is a randomized study of 35 792 pregnancies where a routine anomaly scan using a checklist (skull, neck and brain, face, chest, heart, diaphragm, abdominal wall, stomach, kidneys, bladder, spine and limbs) was carried out at 12 or at 18 weeks (Saltvedt *et al*., 2006). The prenatal detection rate of fetuses with a major abnormality was not significantly different between the 12- and 18-week scan groups (38 vs 47%).

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

The aim of this screening study in more than 45 000 singleton pregnancies is to define the current performance of the 11–13 weeks scan in the detection of fetal non-chromosomal abnormalities.

METHODS

Screening study population

The data for this study were derived from prospective first-trimester screening for aneuploidies at King's College Hospital, London, UK and Medway Maritime Hospital, Gillingham, UK. In this visit, which is held at 11^{+0}–13^{+6} weeks of gestation, we record maternal characteristics and medical history and perform an ultrasound scan to firstly, determine gestational age from the measurement of the fetal CRL (Robinson and Fleming 1975); secondly, measure fetal NT thickness and assess the fetal nasal bone and flow in the ductus venosus and across the tricuspid valve as part of screening for aneuploidies (Snijders *et al*., 1998; Kagan *et al*., 2008) and thirdly, diagnose any major fetal abnormalities. Women are given their estimated individual risk for trisomies 21, 18 and 13 and those considering their risk to be high are offered chorionic villus sampling or amniocentesis for fetal karyotyping.

Data on pregnancy outcome are obtained from the maternity computerized records or the general medical practitioners of the women and are then recorded in our database. All babies in our hospitals are examined in the neonatal period by a pediatrician. Certain asymptomatic internal abnormalities would inevitably have been missed.

This study constitutes a retrospective analysis of data derived from a routine clinical examination and did not require the approval of the ethics committee.

First-trimester anomaly scan

The ultrasound examination is essentially performed transabdominally, using 3–7.5 MHz curvilinear transducers, but in about 1% of cases when there are technical difficulties in obtaining adequate views a transvaginal scan (3–9 MHz) is also carried out. The time allocated for the ultrasound examination of the fetus is 20 min. According to the protocol at the time of the current study, it was aimed to obtain a transverse section of the head to demonstrate the skull, midline echo and the choroid plexuses; a mid-sagittal 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; and transverse and sagittal sections of the trunk and extremities to demonstrate the stomach, bladder, abdominal insertion of the umbilical cord, all the long bones, hands and feet.

Second-trimester anomaly scan

The policy in our hospitals is to offer routinely a second ultrasound examination at 20^{+0}–23^{+6} weeks. This scan is also performed transabdominally and is allocated 20 min for systematic detailed examination of the fetus. In each case, it is aimed to obtain the following views: transverse section of the head at the level of the septum cavum pellucidum and lateral ventricles; sub-occipitobregmatic view to examine the midbrain, cerebellum and vermis; mid-sagittal view of the face to examine the nasal bone and exclude micrognathia; transverse views of the orbits and upper lip; sagittal, coronal and transverse views of the spine; sweep through the heart in transverse plane to include four-chamber view, outflow tracts and three-vessel view; transverse and sagittal sections of the thorax and abdomen to examine the lungs, diaphragm, liver, stomach and bowel, umbilical cord insertion and kidneys, bladder and ureters; systematic examination of upper and lower limbs for length and shape of each bone, position and movement of each joint and examination of both hands and feet, including the digits.

During the study period, all scans were carried out by 1 of 165 sonographers who had obtained the Fetal Medicine Foundation Certificates of Competence in the 11–13 weeks scan and the 18–24 weeks scan or by trainees under the supervision of certified sonographers. All cases of suspected fetal abnormalities were examined by a fetal medicine specialist. Likewise, all cases of suspected fetal cardiac defect were examined by a fetal cardiologist. In addition, the cardiologists carried out fetal echocardiography at 11–14 weeks in those with NT above the 99th percentile and at 20 weeks in those with NT between the 95th and 99th percentiles.

Outcome measures

We included all abnormalities diagnosed prenatally and in the neonatal period. Abnormalities suspected prenatally but not confirmed in the neonates were not

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included. In contrast, the prenatal diagnosis in cases of terminations and miscarriages at less than 24 weeks or stillbirths at or after 24 weeks were assumed to be correct because in these cases postmortem examination was not performed systematically.

Ventriculomegaly was included only if the atrial width during the second or third trimesters was 15 mm or more. Similarly, we included severe hydronephrosis but not mild or moderate pelvicalyceal dilatation. We included all cases of cardiac defects but excluded cases of right aortic arch, persistent left superior vena cava and aberrant right subclavian artery because these are variants of normal rather than true defects. In some of the previous publications, increased NT at 11–13 weeks was reported as cystic hygromas and classified as a defect. We do not consider cystic hygromas to be a distinct entity from enlarged NT and this is not reported as a fetal abnormality (Molina *et al.*, 2006).

Literature search

We searched MEDLINE and EMBASE from 1992 to August 2010 to identify first-trimester screening studies reporting on the ultrasound diagnosis of fetal cardiac and other abnormalities in euploid fetuses. Each article was examined carefully by three of the authors to determine the proportion of major abnormalities diagnosed in the first-trimester scan and the relation of these abnormalities to increased fetal NT. We tried to avoid using duplicate reports of the same subjects and in cases of overlap between publications from the same institution only the largest study was included. In the case of reports of cardiac defects, we excluded functional abnormalities, such as tricuspid regurgitation, and minor defects, such as atrial or ventricular septal defects, because these were not included in all publications.

RESULTS

During the study period (March 2006–September 2009), we carried out an ultrasound examination at 11–13 weeks in 45 191 singleton pregnancies with a live fetus and CRL of 45–84 mm (Figure 1). The median maternal age was 31 (range 14–51) years, the median weight was 66 (range 35–167) kg, the racial origin of the women was Caucasian in 75.4%, African in 16.1%, South Asian in 4.1%, East Asian in 1.9% and mixed in 2.5%.

In 332 (0.7%) of the 45 191 cases, there was prenatal or postnatal diagnosis of aneuploidy and these cases are excluded from the diagnosis of fetal abnormalities (Figure 1). In the 11–13 weeks scan, we diagnosed abnormalities in 213 (0.47%) of the 44 859 cases. In 2003 cases with no abnormalities at the 11–13 weeks scan there was a miscarriage or termination of the pregnancy for psychosocial reasons or the patients were lost to follow-up. In the remaining 42 643 cases, an ultrasound scan was carried out at 20–23 weeks and in 262 (0.6%) of these we diagnosed abnormalities. In 1463 of the 42 381 cases with no abnormalities at the 20–23 weeks scan, there was subsequent fetal death or the patients were lost to follow-up. In the 40 918 cases resulting in live births neonatal examination demonstrated abnormalities in 13 and no defects in 40 905 babies.

Aneuploidies

In 332 cases, fetal aneuploidies were diagnosed by cytogenetic analysis of chorionic villi, amniotic fluid or neonatal blood (Table 1).

In 311 cases, the diagnosis was made before 20 weeks by chorionic villus sampling ($n = 303$) or amniocentesis

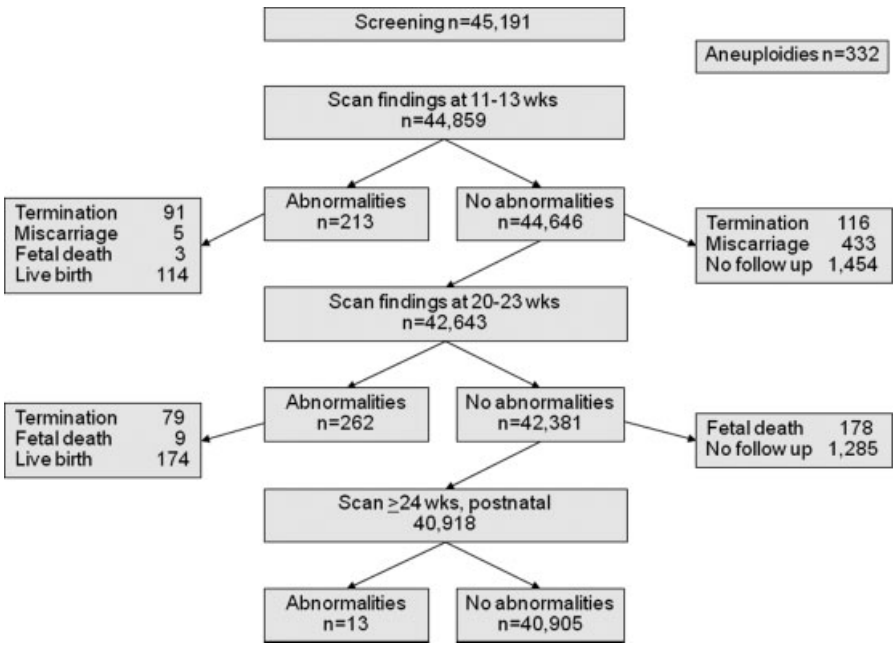

Figure 1—Description of the study population

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Table 1—Diagnosis and outcome of aneuploidies

		Diagnosis			Outcome		
Aneuploidy	Total	<20 weeks	>20 weeks	Postnatal	Termination	Fetal death	Live birth
Trisomy 21	166	155	2	9	148	2	16
Trisomy 18	64	61	3	—	59	5	—
Trisomy 13	30	27	3	—	26	2	2
Turner syndrome	31	31	—	—	26	3	2
Triploidy	19	18	1	—	19	—	—
47, XXX or 47, XXY or 47, XYY	12	12	—	—	7	—	5
Other[a]	10	7	2	1	8	—	2
Total	332	311	11	10	293	12	27

[a] One case each of: trisomy 9; trisomy 22; 46, XY,add(6)(q25); 47, XX +mar.ish der (22); 47, XY,+r(6)dn[9]/46, XY[21]; 46, XX,del(6)(p275); 46, XY,del(18)(p11.2); 46, XX, del(17)(q24.2q24.3); 46, XX,dup(6)(q21q23); DiGeorge.

($n = 8$) because there was a high risk for fetal aneuploidies after first-trimester screening.

In 11 cases, the diagnosis of aneuploidy was made after 20 weeks. In these cases the estimated risk for aneuploidies at first-trimester screening was low but amniocentesis was carried out because fetal defects were detected by the 20–24 weeks scan ($n = 10$) or a third-trimester scan because of suspected fetal growth restriction ($n = 1$). The abnormalities were ventriculomegaly ($n = 2$), hypoplasia of the vermis ($n = 2$), facial cleft ($n = 3$), micrognathia ($n = 2$), cardiac defects ($n = 8$), enlarged echogenic kidneys ($n = 2$), unilateral renal agenesis ($n = 1$), duodenal atresia ($n = 1$), radial aplasia ($n = 1$) and digital defects ($n = 5$).

In ten cases, the diagnosis of aneuploidy was made postnatally. In these cases the estimated risk for aneuploidies at first-trimester screening was either low ($n = 5$) or high ($n = 5$) but the parents declined fetal karyotyping. The second-trimester scan identified a ventricular septal defect in one case but no abnormalities in nine cases.

Diagnosis of fetal abnormalities at 11–13 weeks

All fetal non-cardiac abnormalities in the study population and those diagnosed at 11–13 weeks, including the proportion with fetal NT above the 95th percentile, are summarized in Table 2.

At 11–13 weeks, we diagnosed all cases of acrania/exencephaly, alobar holoprosencephaly, exomphalos, gastroschisis, megacystis (Figure 2) and body stalk anomaly, but none of those with microcephaly, agenesis of the corpus callosum, semilobar holoprosencephaly or hypoplasia of the cerebellum or vermis, cystic adenomatoid malformation or pulmonary sequestration, bowel obstruction, duplex kidneys, severe hydronephrosis or talipes. The correct diagnosis was made in the majority of cases of a missing hand or foot, about half of the cases of diaphragmatic hernia, lethal skeletal dysplasias, isolated shortening of one of the long bones, or polydactyly and about one-tenth of the cases of facial clefts and open *spina bifida*. In two of four cases with infantile polycystic kidney disease, the fetal bladder was not visible at 12 weeks and a repeat scan was carried out at 16 weeks when the bilaterally enlarged hyperechogenic kidneys were noted.

Two types of abnormalities observed at 11–13 weeks subsequently resolved in the majority of cases. There were 20 cases of megacystis with bladder length below 16 mm; in two of these there was miscarriage at 14 weeks, in one case there was development of bilateral severe hydronephrosis by 23 weeks, whereas in the remaining 17 there was spontaneous resolution of the megacystis and the kidneys, ureters and bladder were normal in the 20–23 weeks scan. Similarly, there were 50 cases of exomphalos-containing bowel only and in three of these there was miscarriage or termination of the pregnancy. In 45 (95.7%) of the 47 continuing pregnancies, there was spontaneous resolution of the exomphalos by the 20–23 weeks scan. In contrast, in all cases of exomphalos-containing liver and in those of gastroschisis the condition persisted throughout pregnancy and required surgical correction in the neonatal period.

Diagnosis of cardiac abnormalities at 11–13 weeks

All fetal cardiac abnormalities in the study population and those diagnosed at 11–13 weeks, including the proportion with fetal NT above the 95th percentile, are summarized in Table 3.

At 11–13 weeks, we diagnosed about half of the cases of double outlet right ventricle, hypoplastic left heart and transposition of the great arteries, about one-third of the cases of atrio-ventricular septal defects, coarctation of the aorta, tetralogy of Fallot and pulmonary atresia, but none of the cases of ventricular septal defects, Ebstein anomaly, aortic or pulmonary stenosis, tricuspid atresia and cardiac tumors. In 6 of the 16 cases of ventricular septal defects, the diagnosis was made postnatally. The cardiac tumors included three cases of rhabdomyomas and two of teratomas.

Relation of fetal abnormalities with increased NT thickness

The fetal NT at 11–13 weeks was above the 95th percentile for CRL (Wright *et al*., 2008) in 1922 (4.7%) of

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Table 2—Diagnosis and outcome of non-cardiac abnormalities and their relation to fetal nuchal translucency (NT) thickness above the 95th percentile at the 11–13 weeks scan

Fetal abnormality	Total	NT>95th percentile	Diagnosis			Outcome			First trimester detection in previous studies
			11–13 weeks	20–24 weeks	>24 weeks	TOP	Misc/ IUD	LB	
Neural tube									
Acrania/iniencephaly	29	8 (27.6%)*	29 (100%)	—	—	29	—	—	31/32 (96.9%)
Encephalocele	—	—	—	—	—	—	—	—	2/2 (100%)
Open *spina bifida*	21	1 (4.7%)	3 (14.3%)	18	—	21	—	—	7/19 (36.8%)
Hemivertabrae	1	—	—	1	—	—	—	1	2/3 (66.7%)
Sacrococcygeal teratoma	—	—	—	—	—	—	—	—	1/2 (50.0%)
Brain									
Microcephaly	1	—	—	—	1[a]	—	—	1	0/1 (0.0%)
Craniosynostosis	1	—	—	1	—	1	—	—	0/1 (0.0%)
Corpus callosum agenesis	10	1 (10.0%)	—	10	—	7	1	2	0/1 (0.0%)
Ventriculomegaly	11	—	1 (9.1%)	9	1[b]	9	—	2	3/19 (15.8%)
Holoprosencephaly	—	—	—	—	—	—	—	—	7/9 (77.8%)
Alobar	2	—	2 (100%)	—	—	2	—	—	—
Semilobar	1	—	—	1	—	1	—	—	—
Cerebellar hypoplasia	3	—	—	3	—	3	—	—	5/10 (50.0%)
Vermian agenesis	4	—	—	4	—	3	—	1	—
Face									
Facial cleft	20	3 (15.0%)	1 (5.0%)	19	—	2	1	17	3/23 (13.0%)
Nasopharyngeal teratoma	1	—	—	1	—	—	—	1	0/1 (0.0%)
Micrognathia	1	—	—	1	—	—	—	1	—
Lungs									
Diaphragmatic hernia	8	3 (37.5%)*	4 (50.0%)	4	—	4	—	4	0/4 (0.0%)
Cystic adenomatoid malformation	4	—	—	4	—	—	—	4	0/3 (0.0%)
Extralobar sequestration	2	—	—	2	—	—	—	2	—
Thoracic or abdominal wall									
Ectopia cordis	—	—	—	—	—	—	—	—	1/1 (100%)
Exomphalos	—	—	—	—	—	—	—	—	6/7 (85.7%)
Containing only bowel	50	9 (18.0%)*	50 (100%)	—	—	1	2	47	—
Containing liver	10	1 (10.0%)	10 (100%)	—	—	3	1	6	—
Gastroschisis	19	2 (10.5%)	19 (100%)	—	—	1	—	18	6/7 (85.7%)
Bladder exstrophy	1	—	—	1	—	1	—	—	0/2 (0.0%)
Gastro-intestinal tract									
Esophageal atresia	—	—	—	—	—	—	—	—	0/4 (0.0%)
Duodenal atresia	2	—	—	2	—	—	—	2	1/3 (33.3%)
Bowel obstruction	1	—	—	1	—	—	—	1	—
Anal atresia	—	—	—	—	—	—	—	—	0/1 (0.0%)
Renal									
Megacystis	—	—	—	—	—	—	—	—	6/6 (100%)
Bladder length<16 mm	21	4 (19.0%)*	21 (100%)	—	—	1	2	18	—
Bladder length>16 mm	8	4 (50.0%)*	8 (100%)	—	—	8	—	—	—
Renal agenesis unilateral	6	1 (16.7%)	—	6	—	—	—	6	0/1 (0.0%)
Renal agenesis bilateral	1	—	—	1	—	1	—	—	2/7 (28.6%)
Renal agenesis and multicystic	3	1 (33.3%)	—	3	—	3	—	—	—
Hydronephrosis unilateral	8	—	—	8	—	—	—	8	0/5 (0.0%)
Hydronephrosis bilateral	3	1 (33.3%)	—	3		2	—	1	3/11 (27.3%)
Multicystic dysplasia unilateral	14	—	—	14	—	—	—	14	1/7 (14.3%)
Multicystic dysplasia bilateral	3	1 (33.3%)	—	3	—	3	—	—	—
Infantile polycystic kidneys	6	—	2 (33.3%)	4	—	3	2	1	—
Duplex kidneys	12	—	—	12	—	—	1	11	—
Pelvic kidney	—	—	—	—	—	—	—	—	0/1 (0.0%)
Horseshoe kidney	—	—	—	—	—	—	—	—	0/1 (0.0%)
Skeleton									
Lethal skeletal dysplasia	6	3 (50.0%)*	3 (50.0%)	3	—	5	—	1	3/4 (75.0%)
Achondroplasia	—	—	—	—	—	—	—	—	1/5 (20.0%)
Arthrogryposis	2	—	—	2	—	2	—	—	1/5 (20.0%)
Talipes unilateral	26	1 (3.8%)	—	24	2[a]	—	1	25	2/31 (6.5%)
Talipes bilateral	12	3 (25.0%)*	—	12	—	—	—	12	1/7 (14.3%)
Short long bone unilateral	4	—	2 (50.0%)	2	—	—	—	4	0/3 (0.0%)
Absent hand/or foot	9	—	7 (77.8%)	2	—	4	—	5	1/3 (33.3%)

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Table 2—(*Continued*)

Fetal abnormality	Total	NT>95th percentile	Diagnosis 11–13 weeks	Diagnosis 20–24 weeks	Diagnosis >24 weeks	Outcome TOP	Outcome Misc/ IUD	Outcome LB	First trimester detection in previous studies
Club hand	—	—	—	—	—	—	—	—	1/1 (100%)
Claw hand	—	—	—	—	—	—	—	—	0/1 (0.0%)
Digital defects	—	—	—	—	—	—	—	—	0/14 (0.0%)
Polydactyly	20	—	12 (60.0%)	8	—	—	—	20	—
Ectrodactyly	1	—	—	1	—	—	—	1	—
Other									
Body stalk anomaly	5	5 (100%)*	5 (100%)	—	—	5	—	—	5/5 (100%)
Hydrops fetalis	1	1 (100%)	—	1	—	1	—	—	—
Thyroid goiter	1	—	—	—	1	—	—	1	—
Cloacal defect	1	—	1 (100%)	—	—	—	1	—	—
Ovarian cyst	—	—	—	—	—	—	—	—	0/1 (0.0%)
Hypospadias	—	—	—	—	—	—	—	—	0/9 (0.0%)
Multiple									
Mecker-Gruber syndrome	—	—	—	—	—	—	—	—	2/2 (100%)
Holoprosencephaly, exomphalos	3	3 (100%)*	3 (100%)	—	—	3	—	—	—
Spina bifida, exomphalos	2	—	2 (100%)	—	—	2	—	—	—
Absent hands, TGA	1	1 (100%)*	1 (100%)	—	—	1	—	—	—
Facial cleft, TOF	1	1 (100%)*	1 (100%)	—	—	1	—	—	—
Diaphragmatic hernia, TOF	1	—	—	1	—	1	—	—	—
Vermian agenesis, diaphragmatic hernia	1	1 (100%)*	—	1	—	1	—	—	—
Vermian agenesis, AVSD[c]	1	1 (100%)*	1 (100%)	1	—	—	1	—	—

The last column summarizes the combined data on first-trimester detection of abnormalities in euploid fetuses from ten previous screening studies (Hernadi and Torocsic, 1997; Bilardo *et al*., 1998; D'Ottavio *et al*., 1998; Whitlow *et al*., 1999; Chen *et al*., 2004; Taipale *et al*., 2004; Cedergren and Selbing, 2006; Dane *et al*., 2007; Chen *et al*., 2008; *Oztekin et al.,* 2009).
TOP, termination; Misc, miscarriage <24 weeks; IUD, intrauterine death >24 weeks; LB, live birth; TGA, Transposition of great arteries; TOF, Tetrallogy of Fallot; AVSD, atrio-ventricular septal defect.
[a] Postnatal diagnosis.
[b] Mother was taking warfarin and there was fetal brain hemorrhage at 30 weeks.
[c] The atrio-ventricular septal defect was diagnosed at 11–13 weeks scan and the agenesis of the vermis at 20–24 weeks scan.
* Significance of the difference in proportion of cases with fetal NT >95th percentile in the study group compared to the screening population examined by χ^2 test, $p < 0.05$.

the 40 905 cases, resulting in phenotypically normal live births. Significantly increased incidence of NT above the 95th percentile was observed in cases of acrania ($p < 0.0001$), diaphragmatic hernia ($p = 0.007$), exomphalos ($p < 0.001$), megacystis ($p < 0.0001$), lethal skeletal dysplasia ($p = 0.0002$), bilateral talipes ($p = 0.012$), body stalk anomaly ($p < 0.0001$) and in cases with multiple defects ($p < 0.0001$).

There were 106 cases with cardiac abnormalities, including four with additional defects. The fetal NT was above the 95th percentile in 30 (28.3%), which is significantly higher than in the phenotypically normal live births ($p < 0.0001$). The incidence of increased NT was 35.3% (30 of 85) cases of major cardiac abnormalities, after exclusion of the 16 cases of ventricular septal defects and the 5 cases of cardiac tumors that developed in the second trimester. The NT was increased in 18 (64.3%) of the 28 fetuses with cardiac abnormalities diagnosed at 11–13 weeks compared to 12 (15.4%) of the 78 diagnosed in the second trimester or postnatally ($p \leq 0.0001$).

Review of the literature

The literature search identified 24 first-trimester screening studies for cardiac and/or non-cardiac abnormalities.

Table 4 summarizes the results of 15 screening studies providing data on the prevalence of cardiac and non-cardiac abnormalities in the study populations and the proportion of those detected in the first-trimester scan. In these 15 studies, all abnormalities were classified by the authors as being major. Most studies included isolated cystic hygromas as major abnormalities and most studies included fetuses with aneuploidies. The overall prevalence of abnormalities was 1.6% (range 0.7–2.8%) and 40.8% (range 12.5–83.7%) of these were detected in the first trimester. There was another screening study that we did not include in this table because the authors acknowledged that they had a mixture of major and minor abnormalities but they did not specify which ones they considered to be major (Carvalho *et al*., 2002). The combined data on specific groups of abnormalities and their early detection in euploid fetuses from 10 of the above 15 studies that provided such details are presented in Table 2. Details from the individual studies are presented in supplementary Table S1. In total, there were 288 fetuses with abnormalities and 101 (35.1%) of these were detected in the first-trimester scan. Early diagnosis was made in most cases of acrania, holoprosencephaly, exomphalos, gastroschisis, megacystis and body stalk anomaly, but in less than one-third of cases of *spina bifida*.

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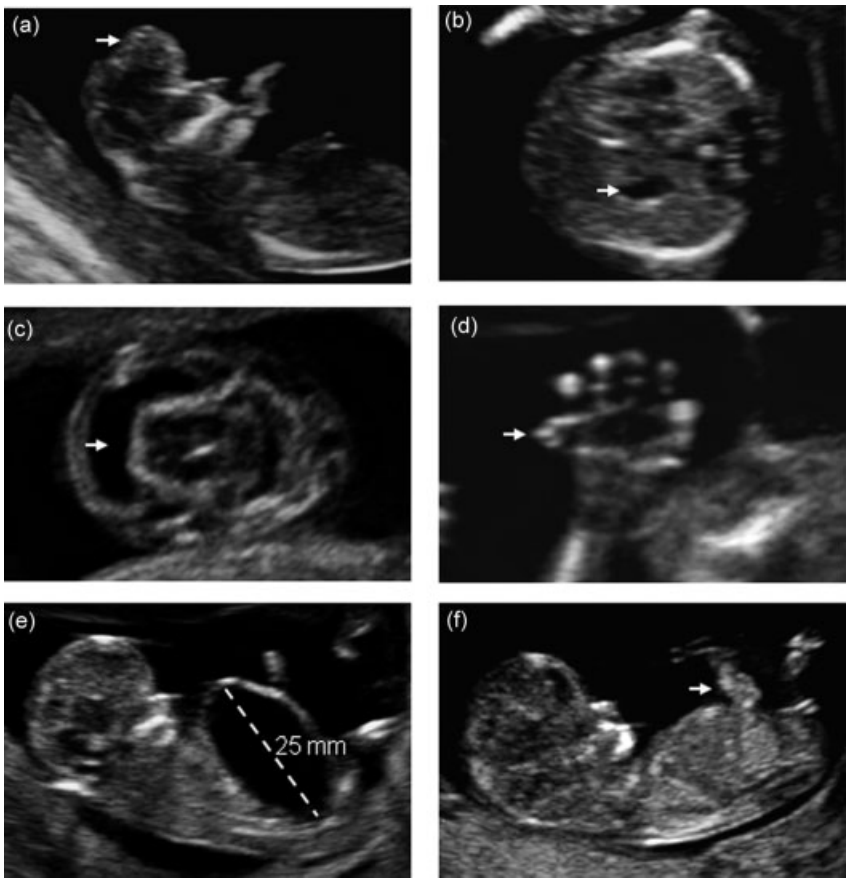

Figure 2—Fetal abnormalities at 11–13 weeks. (a) Acrania with distorted brain (arrow), (b) diaphragmatic hernia with intrathoracic herniation of the stomach (arrow), (c) alobar holoprosencephaly with single lateral ventricle (arrow), (d) postaxial polydactyly with the arrow pointing at the sixth digit, (e) severe megacystis with longitudinal bladder length of 25 mm and (f) exomphalos containing bowel only (arrow)

Table 5 summarizes the results of 20 screening studies providing data on the prevalence of cardiac abnormalities in the study populations and the proportion of those detected in the first-trimester scan. In most of these studies, all abnormalities were classified by the authors as being major. However, in our analysis of their results, we excluded abnormalities that we considered as minor so that the results of the studies can be comparable. Most studies included only euploid fetuses but in four there were fetuses with aneuploidies. Most studies provided data on the association of cardiac abnormalities with increased NT. However, the studies varied in their definition of what constituted increased NT, which was observed in 73 (33.0%) of the 221 cases with available data. The combined data on specific groups of cardiac abnormalities and their early detection in euploid fetuses from 11 of the above 20 studies that provided such details are presented in Table 3. Details from the individual studies are presented in supplementary Table S2. In total, there were 152 defects and 10 (6.6%) of these were detected in the first-trimester scan. The early detection rate for the most common cardiac abnormalities varied from about 20% for hypoplastic left heart to 10% for coarctation of the aorta, 5% for tetralogy of Fallot and ventricular septal defect and 0% for transposition of the great arteries.

DISCUSSION

The findings of this study and the results of our analysis of previous screening studies highlight that major fetal abnormalities fall into essentially three groups in relation to whether they can be detected at the 11–13 weeks scan. Some abnormalities, such as anencephaly, should always be detected and others, such as microcephaly, will never be. A third group includes abnormalities that are potentially detectable depending on firstly, the objectives set for such a scan and consequently the time allocated for the fetal examination, the expertise of the sonographer and the quality of the equipment used; secondly, the presence of an easily detectable marker for an underlying abnormality and thirdly, the evolution in the phenotypic expression of the abnormality with gestation.

An advantage of early rather than late diagnosis of major abnormalities, which are either lethal or associated with severe handicap, is that the parents are provided with the option of earlier and safer pregnancy termination. However, in some cases, such as lethal skeletal dysplasia, early surgical termination may prevent diagnosis of the underlying condition and therefore accurate counselling of the parents as to the risk of recurrence.

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Table 3—Diagnosis and outcome of cardiac abnormalities and their relation to fetal nuchal translucency (NT) thickness above the 95th percentile at 11 to 13 weeks scan

			Diagnosis				Outcome			
			11–13 wks							
Cardiac abnormalities	Total	NT >95th percentile	*n*	NT>95th percentile	20–24 weeks	>24 weeks	TOP	Misc/ IUD	LB	First-trimester detection in previous studies
Coarctation of the aorta (CoA)	15	4 (26.7%)*	4 (26.7%)	2 (50.0%)	10	1	3	1	11	2/21 (9.5%)
Tetrallogy of Fallot (TOF)	10	4 (40.0%)*	3 (30.0%)	2 (66.7%)	7	—	2	—	8	1/21 (4.8%)
Hypoplastic left heart	10	4 (40.0%)*	5 (50.0%)	2 (40.0%)	5	—	8	—	2	4/19 (21.1%)
Atrioventricular septal defect (AVSD)	9	3 (33.3%)*	3 (33.3%)	3 (100%)	6	—	3	—	6	0/12 (0.0%)
Double outlet right ventricle (DORV)	7	5 (71.4%)*	4 (57.1%)	3 (75.0%)	3	—	5	—	2	0/2 (0.0%)
Ebstein anomaly	5	1 (20.0%)	—	—	5	—	1	—	4	0/3 (0.0%)
Transposition of the great arteries	5	—	2 (40.0%)	—	3	—	1	1	3	0/18 (0.0%)
Pulmonary stenosis	5	1 (20.0%)	—	—	5	—	—	—	5	0/9 (0.0%)
Pulmonary atresia (PA)	3	2 (66.7%)*	1 (33.3%)	1 (100%)	2	—	3	—	—	0/1 (0.0%)
Tricuspid atresia	1	—	—	—	1	—	1	—	—	0/3 (0.0%)
Tricuspid dysplasia	1	1 (100%)*	1 (100%)	1 (100%)	—	—	1	—	—	—
Aortic stenosis	1	—	—	—	1	—	1	—	—	1/5 (20.0%)
CoA and AVSD	1	—	—	—	1	—	1	—	—	—
CoA and VSD	1	—	—	—	1	—	—	—	1	—
TOF and PA	1	1 (100%)*	—	—	1	—	1	—	—	—
TOF and AVSD	1	—	—	—	1	—	—	—	1	—
Left atrial isomerism	1	—	1 (100%)	—	—	—	1	—	—	—
Double inlet left ventricle (DILV)	1	—	—	—	1	—	—	—	1	0/1 (0.0%)
DORV and PA	1	1 (100%)*	1 (100%)	1 (100%)	—	—	1	—	—	—
PA, TGA and DILV	1	—	—	—	1	—	—	—	1	—
DORV, PA and AVSD	1	—	—	—	1	—	1	—	—	—
Anomalus pulmonary venous return	—	—	—	—	—	—	—	—	—	0/2 (0.0%)
Mitral atresia	—	—	—	—	—	—	—	—	—	0/1 (0.0%)
Interrupted aortic arch	—									0/1 (0.0%)
Common truncus arteriosus	—	—	—	—	—	—	—	—	—	0/1 (0.0%)
Ventricular septal defect (VSD)	16	—	—	—	10	6[a]	—	1	15	2/32 (6.3%)
Cardiac tumor	5	—	—	—	4	1	2	1	2	—
Multiple (Table 2)	4	3 (75.0%)*	3 (75.0%)	3 (100%)	1	—	3	1	—	—
Total	106	30 (28.3%)*	28 (26.4%)	18 (64.3%)	70	8	39	5	62	10/152 (6.6%)

The last column summarizes the combined data on first-trimester detection of abnormalities in euploid fetuses from ten previous screening studies (Hernadi and Torocsic, 1997; *Bilardo et al.,* 1998; D'Ottavio *et al*., 1998; Hyett *et al*., 1999; Mavrides *et al*., 2001; Michailidis and Economides, 2001; Chen *et al*., 2004; Taipale *et al*., 2004; Cedergren and Selbing, 2006; Dane *et al*., 2007; Chen *et al*., 2008). TOP, termination; Misc, miscarriage<24 weeks; IUD, intrauterine death >24 weeks; LB: live birth.

[a] In all six cases, the diagnosis was made postnatally.

* Significance of the difference in proportion of cases with fetal NT>95th percentile in the study group compared to the screening population examined by χ^2 test, $p < 0.05$.

Always detectable abnormalities

A basic ultrasound scan which aims to obtain the appropriate mid-sagittal view of the fetus for measurement of the CRL and NT and transverse sweeps through the head and abdomen should identify all cases of body stalk anomaly, anencephaly, alobar holoprosencephaly, exomphalos, gastroschisis and megacystis.

Body stalk anomaly is characterized by the presence of a major abdominal wall defect, severe kyphoscoliosis, short umbilical cord and rupture of the amniotic membranes so that half of the body lies in the amniotic cavity and the other half in the celomic cavity (Daskalakis *et al*., 1997). In this and previous screening studies, all cases of body stalk anomaly were detected in the first-trimester scan.

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Table 4—Screening studies reporting on the effectiveness of the first-trimester scan in the diagnosis of fetal cardiac and non-cardiac abnormalities

Author	Total	Scan route	GA (weeks)	Fetal abnormalities			
				Total	Cystic hygromas	Aneuploidy	Detected
Hernadi and Torocsic, 1997	3991	TA, TV	11–14	49 (1.2%)	7 (14.3%)	4 (8.2%)	20 (40.8%)
D'Ottavio *et al*., 1998	4078	TV	13–15	88 (2.2%)	30 (34.1%)	19 (21.6%)	54 (61.4%)
Bilardo *et al*., 1998	1690	TA, TV	10–14	23 (1.4%)	3 (13.0%)	—	10 (43.5%)
Hafner *et al*., 1998	4233	TA	10–13	56 (1.3%)	—	—	7 (12.5%)
Whitlow *et al*., 1999[a]	6443	TA, TV	11–14	63 (1.0%)	14 (22.2%)	14 (22.2%)	37 (58.7%)
Guariglia and Rosati, 2000	3478	TV	10–16[b]	57 (1.6%)	15 (26.3%)	8 (14.0%)	33 (57.9%)
Taipale *et al*., 2004	4789	TV	10–16[c]	33 (0.7%)	—	4 (12.1%)	6 (18.2%)
Chen *et al*., 2004	1609	TA, TV	12–14	26 (1.6%)	1 (3.8%)	11 (42.3%)	14 (53.8%)
Becker and Wegner, 2006	3094	TA, TV	11–13	86 (2.8%)	—	56 (65.1%)	72 (83.7%)
Cedergren and Selbing, 2006	2708	TA	11–14[d]	32 (1.2%)	3 (9.4%)	1 (3.1%)	13 (40.6%)
Saltvedt *et al*., 2006	18053	TA	11–14	371 (2.1%)	Not stated	—	74 (19.9%)
Dane *et al*., 2007	1290	TA	11–14	24 (1.9%)	3 (12.5%)	5 (20.8%)	17 (70.8%)
Chen *et al*., 2008	7642	TA	10–14	127 (1.7%)	30 (23.6%)	32 (25.2%)	51 (40.2%)
Oztekin *et al*., 2009	1805	TA	11–14	21 (1.2%)	3 (14.3%)	—	14 (66.7%)
Ebrashy *et al*., 2010	2876	TA, TV	13–14	31 (1.1%)	7 (22.6%)	—	21 (67.7%)
Total	67779	—	10–16	1087 (1.6%)	116 (10.7%)	154 (14.2%)	443 (40.8%)

In all studies the abnormalities according to the authors were classified as major. Most studies classified isolated cystic hygromas as major abnormalities and most studies included fetuses with aneuploidies.
GA, gestational age, TV, transvaginal; TA, transabdominal.
[a] Includes all data from Economides and Braithwaite, 1998.
[b] 25% of the population were above 14 weeks.
[c] 10% of the population were above 14 weeks.
[d] 15% of the population were above 14 weeks.

In the 11–13 weeks scan, the pathognomonic feature of anencephaly is acrania with the brain appearing either normal or at varying degrees of distortion and disruption. In the first phase of a multicenter study of screening for aneuploidies by measurement of fetal NT in the early 1990s 34 830 fetuses were examined and diagnosis of anencephaly was made in only 74% (23 of 31) of the affected fetuses (Johnson *et al*., 1997). Subsequently, the sonographers were informed of the different diagnostic features of anencephaly in the first compared to the second trimester and they were instructed to specifically look for and record the presence or absence of acrania. In the second phase of the study, 20 407 fetuses were examined and all 16 cases of anencephaly were diagnosed at the early scan (Johnson *et al*., 1997).

The diagnosis of alobar holoprosencephaly is based on the fusion of the anterior horns of the lateral ventricles and the absence of the butterfly sign in a cross-sectional view of the fetal brain (Sepulveda *et al*., 2004). In 66% of cases diagnosed in the first trimester there is an underlying aneuploidy, mainly trisomy 13 (Kagan *et al*., 2010). In this and most of the previous first-trimester screening studies, all cases of alobar holoprosencephaly were detected.

Megacystis with bladder length below 16 mm and exomphalos-containing bowel only constitute a subgroup of the always detectable abnormalities because the defect is usually transient. Megacystis at 11–13 weeks, defined by bladder length of 7 mm or more, is found in about 1 in 1500 pregnancies and in about 30% of cases there is an associated aneuploidy, mainly trisomy 13 or 18 (Sebire *et al*., 1996; Kagan *et al*., 2010). In the euploid group, the prognosis depends on bladder length; in 90% of cases with bladder length below 16 mm there is spontaneous resolution of the megacystis, whereas in those with bladder length of 16 mm or more there is usually progression to severe obstructive uropathy (Liao *et al*., 2003). Similarly, in about half of the fetuses with exomphalos diagnosed at 11–13 weeks there is an associated aneuploidy, mainly trisomy 18 (Kagan *et al*., 2010). In the euploid group, there is spontaneous resolution of the exomphalos in about 95% of cases if the sac contains only bowel. In contrast, if the contents include liver the exomphalos persists throughout pregnancy and requires surgical correction in the neonatal period. In cases of gastroschisis, the risk of aneuploidies is not increased but in all cases the condition persists throughout pregnancy.

Undetectable abnormalities

Certain fetal abnormalities are manifested only during the second or third trimester of pregnancy and are therefore impossible to detect at 11–13 weeks. One such abnormality is microcephaly, in the absence of holoprosencephaly or other brain defects, which is usually diagnosed after 30 weeks from the disproportionately small measurement of the fetal head circumference. The corpus callosum normally develops at 14–19 weeks (Ren *et al*., 2006) and inevitably the diagnosis of agenesis of the corpus callosum cannot be made at 11–13 weeks. Similarly, ventriculomegaly secondary to congenital infection or brain hemorrhage will be manifested after

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Table 5—Screening studies reporting on the effectiveness of the first-trimester scan in the diagnosis of major fetal cardiac abnormalities

					Major cardiac abnormalities				
								Increased NT	
Author	Total	Scan route	GA (weeks)	Exclusion minor defects	Prevalence	Aneuploidies	Early detection	Cut-off	Prevalence
Hernadi and Torocsic, 1997	3991	TA, TV	11–14	2	1 (0.02%)	—	—	—	Not given
D'Ottavio *et al.*, 1998	4078	TV	13–14	2	12 (0.29%)	—	3 (25.0%)	—	Not given
Bilardo *et al.*, 1998	1690	TA, TV	10–14	—	4 (0.23%)	—	—	3.0 mm	2 (50.0%)
Hafner *et al.*, 1998	4233	TA	10–13	5	14 (0.33%)	—	1 (7.1%)	2.5 mm	4 (28.6%)
Hyett *et al.*, 1999	29154	TA	10–14	7	43 (0.15%)	—	1 (2.3%)	95th percentile	25 (58.1%)
Schwarzler *et al.*, 1999	4523	TA	10–14	2	9 (0.20%)	—	—	2.5 mm	1 (11.1%)
Mavrides *et al.*, 2001[a]	7339	TA	10–14	2	24 (0.33%)	—	4 (16.7%)	2.5 mm	4 (16.7%)
Michailidis and Economides, 2001	6650	TA, TV	10–14	2	9 (0.14%)	—	2 (22.2%)	95th percentile	2 (22.2%)
Orvos *et al.*, 2002	4309	TV	10–13	7	32 (0.74%)	—	—	3.0 mm	16 (53.3%)[b]
Taipale *et al.*, 2004	4789	TV	10–16[c]	7	18 (0.38%)	—	1 (5.6%)	3.0 mm	4 (22.2%)
Chen *et al.*, 2004	1609	TA, TV	12–14	5	7 (0.44%)	4 (57.1%)	4 (57.1%)	—	Not given
Bahado-Singh *et al.*, 2005	8167	TA	10–14	15	6 (0.07%)	—	—	2.5 mm	3 (50.0%)
Bruns *et al.*, 2006	3664	?	11–14	11	9 (0.25%)	—	—	95th percentile	2 (22.2%)
Becker and Wegner, 2006	3094	TA, TV	11–14	—	11 (0.36%)	—	6 (54.5%)	2.5 mm	6 (54.5%)
Cedergren and Selbing, 2006	2708	TA	11–14	6	3 (0.11%)	—	—	—	Not given
Dane *et al.*, 2007	1290	TA	11–14	—	1 (0.08%)	—	—	—	Not given
Westin *et al.*, 2007[d]	16260	TA	12–14	—	29 (0.18%)	—	—	3.0 mm	2 (6.9%)
Muller *et al.*, 2007	4144	TA	10–14	—	13 (0.31%)	—	—	99th percentile	2 (15.4%)
Chen *et al.*, 2008	7642	TA	10–14	13	19 (0.25%)	10 (52.6%)	7 (36.8%)	—	Not given
Oztekin *et al.*, 2009	1805	TA	11–14	1	2 (0.11%)	—	—	95th percentile	0 (0.0%)
Total	121139		10–16	87	266 (0.22%)	14 (5.3%)	29 (10.9%)	—	73/221 (33.0%)

In some of the studies, the authors included minor defects (atrial or ventricular septal defect) and functional abnormalities (tricuspid or aortic regurgitation) and in this analysis we have excluded these abnormalities.

GA, gestational age, TV, transvaginal; TA, transabdominal; NT, nuchal translucency.

[a] Includes the data published by Carvalho *et al.*, 2002 (not shown) and 25% of data of Schwarzler *et al.*, 1999.

[b] NT available in 30 of the 32 fetuses with cardiac defects.

[c] 10% of the population were above 14 weeks.

[d] Includes all data published by Westin *et al.*, 2006.

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the event, usually in the second or third trimesters. The same would be true for fetal tumors, including nasopharyngeal, cardiac and sacrococcygeal teratomas, which mostly develop after the first trimester. Ovarian cysts usually develop in the third trimester.

The earliest reported gestation for the diagnosis of echogenic lesions of the lungs, including sequestration and cystic adenomatoid malformation, is 16 weeks (Cavoretto *et al*., 2008). Presumably, production of pulmonary fluid and its retention within the abnormally developed lung resulting in detectable hyperechogenicity occurs after the onset of the canalicular phase of lung development at 16 weeks.

Similarly, the diagnosis of duodenal atresia and bowel obstruction is not through direct visualization of the defect but by detecting their manifestations of polyhydramnios and double-bubble appearance of the stomach and proximal duodenum for the first and distended loops of bowel proximal to the obstruction for the second. Bowel distention and polyhydramnios develop only when the amount of swallowed amniotic fluid exceeds the absorptive capacity of the stomach and proximal duodenum and this usually occurs after 20 weeks. The daily volume of amniotic fluid swallowed by the fetus increases exponentially with gestation from about 10 mL at 20 weeks to 850 mL at term (Pritchard, 1966).

Most cases of severe hydronephrosis due to ureteric stenosis or vesicoureteric reflux, unlike those from urethral obstruction presenting as megacystis, are not apparent until the second or third trimesters. The most likely explanation for this delayed diagnosis is that in early pregnancy the rate of fetal urine production is too low to result in retention within the upper urinary tract. The estimated rate of urine production increases exponentially with gestation from 5 mL/h at 20 weeks to 50 mL/h at 40 weeks (Rabinowitz *et al*., 1989).

Potentially detectable

In our study, the primary objective of the 11–13 weeks scan was to provide routine first-trimester screening for aneuploidies in two major maternity units with a combined total of more than 10 000 deliveries per year. Basic assessment of the fetal anatomy was carried out through a series of sagittal and transverse views, which included examination of the brain at the level of the choroid plexuses but not the posterior fossa, evaluation of the spine for major degrees of kyphoscoliosis but not systematic examination of individual vertebrae for evidence of *spina bifida*, assessment of the nasal bone but not the upper lip and maxilla, examination of the four-chamber view of the heart, as part of recording blood flow across the tricuspid valve, but not the outflow tracts, demonstration of the stomach, bladder, limbs, hands and feet but not systematic measurement of long bones. It is therefore not surprising that most or all cases of posterior fossa defects, *spina bifida*, facial cleft, cardiac and renal defects were missed, whereas most cases of absent hands or feet and polydactyly were detected.

In some of the abnormalities, such as facial cleft, renal agenesis and multicystic kidneys, improved first trimester detection will be achieved if firstly, detailed examination of the relevant structure is included in the protocol; secondly, the sonographers receive appropriate training for such examination, they are given extra time for the scan and resort to vaginal sonography more often than in current practice and thirdly, new techniques are described which facilitate the diagnosis of specific conditions. A good example that is likely to facilitate the diagnosis of facial cleft is assessment of the retronasal triangle (Sepulveda *et al*., 2010).

Appropriate training of sonographers, extra time allocated to the scan and inclusion of detailed examination of the heart in the protocol, could be applied for improved detection of cardiac abnormalities. However, as demonstrated by the experience with the second trimester scan in the last 30 years, effective diagnosis ultimately depends on the examination being carried out by an expert in fetal echocardiography and the major challenge in routine scanning is to identify an easily recognizable marker of the high-risk group that can then be referred to the expert. A good example of such a marker in the first trimester is high NT which was observed in about 65% of the fetuses with cardiac defects diagnosed in the first trimester compared to 15% in those diagnosed in the second. Increased NT was found in 35% of our fetuses with major cardiac defects. Further improvements in early diagnosis of cardiac defects will therefore necessitate the inclusion of additional markers; abnormal blood flow through the tricuspid valve and ductus venosus are currently under investigation to determine their usefulness as such markers. However, some cardiac defects may not be detectable at 11–13 weeks even by experts. For example, in some cases we have observed progression from a fairly normal heart in early pregnancy to hypoplastic left heart or pulmonary atresia during the second trimester.

Other abnormalities that can be unmasked by the presence of high NT are lethal skeletal dysplasia and diaphragmatic hernia. In these conditions, high NT was substantially more prevalent in the cases diagnosed in the first than in the second trimester. It is likely that early diagnosis of these abnormalities was the consequence of a detailed examination of the fetal anatomy either by the sonographer performing the routine scan or by a fetal medicine expert whose advice was sought because of the detection of the high NT. Another hypothesis for the association between early diagnosis of an abnormality with high NT is that there is a wide spectrum of phenotypic expression of a given condition and it is the ones at the more severe end of the spectrum, and therefore amenable to earlier diagnosis, that are more likely to cause the necessary hemodynamic changes leading to increased NT. For example, in the case of diaphragmatic hernia, increased NT, presumably due to venous congestion in the head and neck, would be observed only in those cases where intrathoracic herniation of the abdominal viscera occurs in the first trimester, rather than later in pregnancy. Alternatively, in all cases of diaphragmatic hernia, there is intrathoracic herniation in the first trimester but increased NT is observed only

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with the larger lesions which produce more severe mediastinal compression (Sebire *et al*., 1997). Similar arguments could be advanced for explaining the association between high NT and certain cardiac defects, such as hypoplastic left heart and coarctation of the aorta. It is possible that increased NT is observed in the most severe cases of these lesions.

A recently described marker that may improve the currently low detection rate of open *spina bifida* at 11–13 weeks is the abnormal posterior fossa observed in the same mid-sagittal view of the fetal face as for measurement of fetal NT and assessment of the nasal bone (Chaoui *et al*, 2009; Lachmann *et al*., 2011). Open *spina bifida* is associated with caudal displacement of the brain stem and compression of the fourth ventricle–cisterna magna complex within the confined space between the sphenoid and occipital bones. It is possible that examination of the posterior fossa may also lead to the detection of at least some of the cases of cerebellar and vermian hypoplasia that are now missed in the first-trimester scan.

The role of the 11–13 weeks scan as an effective method of screening for aneuploidies is now well established. This study has demonstrated that the 11–13 weeks scan can also identify many non-chromosomal major abnormalities but the provision of a summary statistic on performance is meaningless. Some abnormalities should always be detected and others will never be. The performance, however, for most abnormalities ultimately depends on their association with easily detectable markers and a policy decision as to the objectives of the scan and the necessary allocation of resources for achieving such objectives.

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