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Diagnosis of major heart defects by routine first-trimester ultrasound examination: association with increased nuchal translucency, tricuspid regurgitation and abnormal flow in ductus venosus

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KEYWORDS: congenital heart defect; ductus venosus Doppler; fetal abnormalities; first-trimester screening; nuchal translucency; prenatal diagnosis; tricuspid regurgitation; ultrasound examination

CONTRIBUTION

What are the novel findings of this work?
This study demonstrates that more than half of major heart defects can be detected by routine ultrasound examination at 11–13 weeks' gestation and confirms that increased nuchal translucency, tricuspid regurgitation and abnormal flow in the ductus venosus are useful markers for such defects.

What are the clinical implications of this work?
At 11–13 weeks' gestation, measurement of nuchal translucency and assessment of flow across the tricuspid valve and in the ductus venosus can lead to early diagnosis of major heart defect.

ABSTRACT

Objective *To examine the association between fetal major heart defects and increased nuchal translucency thickness (NT), tricuspid regurgitation and abnormal flow in the ductus venosus in a large population of singleton pregnancies undergoing routine ultrasound examination at 11–13 weeks' gestation.*

Methods *This was a retrospective study of prospectively collected data from singleton pregnancies attending for a routine ultrasound scan at 11–13 weeks' gestation, which included examination of fetal anatomy, measurement of NT and assessment of blood flow across the tricuspid valve and in the ductus venosus, according to a standardized protocol. The incidence of fetal NT $\geq 95^{th}$ and $\geq 99^{th}$ percentiles, tricuspid regurgitation and reversed a-wave in the ductus venosus in fetuses with and those without a major heart defect was determined and the performance of each marker and their combination in the detection of major heart defects was calculated.*

Results *The study population of 93 209 pregnancies with no apparent chromosomal abnormality included 211 (0.23%) with a fetal major heart defect and 92 998 morphologically normal neonates. In 113 (53.6%) cases with a major heart defect, the diagnosis was made at the 11–13-week scan, in 82 (38.9%) at the 18–24-week scan, in 10 (4.7%) at the third-trimester scan and in six (2.8%) postnatally. At the 11–13-week scan, we diagnosed all cases of tricuspid or pulmonary atresia and polyvalvular dysplasia, > 90% of cases of hypoplastic left heart syndrome or atrioventricular septal defect, about 60% of complex heart defects and cases of left atrial isomerism (interrupted inferior vena cava with normal intracardiac anatomy), 30–40% of cases of tetralogy of Fallot and arch abnormalities, 25% of tricuspid valve abnormalities and about 15% of cases of transposition of the great arteries, but none of aortic or pulmonary stenosis or common arterial trunk. Fetal NT $\geq 95^{th}$ or $\geq 99^{th}$ percentile, tricuspid regurgitation or abnormal ductus venosus flow was observed in 77 (36.5%), 45 (21.3%), 61 (28.9%) and 58 (27.5%) fetuses with a major heart defect, respectively, and in 5678 (6.1%), 857 (0.9%), 1136 (1.2%) and 1644 (1.8%) of those without a heart defect. Any one of NT $\geq 95^{th}$ percentile, tricuspid regurgitation or abnormal flow in the ductus venosus was found in 117 (55.5%; 95% CI, 48.5–62.3%) fetuses with*

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a heart defect and in 8166 (8.8%; 95% CI, 8.6–9.0%) of those without a heart defect. Any one of NT ≥ 99th percentile or the other two markers was found in 99 (46.9%; 95% CI, 40.0–53.9%) fetuses with a heart defect and in 3517 (3.8%; 95% CI, 3.7–3.9%) of those without a heart defect.

Conclusion *At 11–13 weeks' gestation, measurement of fetal NT and assessment of flow across the tricuspid valve and in the ductus venosus can lead to early diagnosis of major heart defect.*

INTRODUCTION

Ultrasound examination at 11–13 weeks' gestation can lead to the diagnosis of a wide range of fetal non-chromosomal abnormalities[1–3]. In relation to the first-trimester scan, fetal non-chromosomal abnormalities can be subdivided into three groups[2,3]: first, those that are easily detectable by direct visualization, such as acrania and exomphalos; second, those that are potentially detectable depending on the objectives set for such a scan based on a standardized protocol and the presence of easily detectable markers for an underlying abnormality, such as increased nuchal translucency thickness (NT), and tricuspid regurgitation and abnormal flow in the ductus venosus for heart defects[4–12]; and, third, those that are undetectable in the first trimester because they develop later in pregnancy, such as ovarian cysts, or their phenotypic expression becomes apparent in later pregnancy as a result of physiological changes in the fetus, such as increased fetal swallowing unmasking bowel obstruction, or defects which evolve with advancing gestational age, such as short limbs in achondroplasia.

In a previous study of first-trimester screening for aneuploidy in 40 990 singleton pregnancies, examined between 2006 and 2009, we reported that fetal NT > 95th percentile, tricuspid regurgitation or reversed a-wave in the ductus venosus was observed in 58% (95% CI, 47–68%) of 85 fetuses with a major heart defect, and in 8% of those without a heart defect, and suggested that these biomarkers are useful in the early diagnosis of heart defects[10,11].

The objectives of this study of 93 209 singleton pregnancies undergoing routine examination of fetal anatomy was to investigate further the association between fetal major heart defects and increased NT, tricuspid regurgitation and abnormal flow in the ductus venosus at the 11–13-week scan.

METHODS

Study population

This was a retrospective study of prospectively collected data from women with a singleton pregnancy attending for a routine hospital visit at 11 + 0 to 13 + 6 weeks' gestation at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK, between October 2009 and July 2018. At this visit, we recorded maternal characteristics and medical history, performed an ultrasound scan to, first, measure fetal NT[13–15], second, diagnose any fetal abnormalities[2,3], and, third, assess blood flow across the tricuspid valve and in the ductus venosus[8,10,11]. Assessment of risk for aneuploidy included measurement of maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A[16,17]. Women were given their estimated individual risk for trisomy, and those with a high risk were offered invasive testing for fetal karyotyping or cell-free DNA testing for trisomies 21, 18 and 13[18,19].

In all cases with a continuing pregnancy, a fetal anomaly scan was undertaken at 18–24 weeks' gestation and, in many cases, a scan was also carried out at 30–34 or 35–37 weeks' gestation. We excluded pregnancies with known aneuploidy. Data on pregnancy outcome were collected from computerized records of the delivery ward and neonatal unit or the patients' general practitioners, and all prenatal and postnatal findings were recorded in a fetal database. This study constitutes a retrospective analysis of data derived from routine clinical examination and did not require ethical committee approval.

Ultrasound examination

All ultrasound examinations were carried out according to standardized protocols by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in ultrasound examination for fetal abnormalities or by trainees under the supervision of certified sonographers. The ultrasound examinations were performed transabdominally, using a 3–7.5-MHz curvilinear transducer, but, in 2–3% of cases, when there were technical difficulties in obtaining adequate views, a transvaginal scan (3–9 MHz) was also carried out. The time allocated for the ultrasound examination of the fetus was 30 min. All cases of suspected fetal abnormality at the first-, second- or third-trimester scan were examined on the same day by a fetal medicine specialist. Likewise, all cases of suspected fetal heart defect were examined by a fetal cardiologist.

At the 11–13-week scan, the protocol included a transverse section of the thorax and use of color Doppler to assess the four-chamber view of the heart and outflow tracts and blood flow across the tricuspid valve and in the ductus venosus. At the routine second- and third-trimester scans, the protocol included a sweep through the heart in the transverse plane to assess the four-chamber view, outflow tracts and three-vessel view.

Presence or absence of tricuspid regurgitation was determined by pulsed-wave Doppler during fetal quiescence[20]. A Doppler sample volume of 3.0 mm was positioned across the tricuspid valve and partially in the right atrium in an apical four-chamber view of the fetal heart such that

the angle with the direction of flow was less than 30°. The tricuspid valve could be insufficient in one or more of its three cusps and therefore the sample volume was placed across the valve at least three times in an attempt to interrogate the complete valve. The diagnosis of tricuspid regurgitation was made if it was found during at least half of the systole and with a velocity of > 60 cm/s. Care was taken not to misinterpret with the aortic flow overlap, which has a much slower (30–50 cm/s) flow pattern at this early gestational age. In the assessment of flow in the ductus venosus[21], examinations were undertaken during fetal quiescence. The magnification of the image was such that the fetal thorax and abdomen occupied the whole screen, a right ventral midsagittal view of the fetal trunk was obtained, and color flow mapping was used to demonstrate the umbilical vein, ductus venosus and fetal heart. The pulsed Doppler sample was small (0.5–1.0 mm) to avoid contamination from the adjacent veins and it was placed in the yellowish aliasing area which is the portion immediately above the umbilical sinus. The insonation angle was less than 30°, the filter was set at a low frequency (50–70 Hz) to allow visualization of the whole waveform, and the sweep speed was high (2–3 cm/s) so that the waveforms were spread widely, allowing better assessment of the a-wave. Waveforms were assessed qualitatively and considered to be abnormal if the a-wave was reversed.

Fetal echocardiography was carried out by a cardiologist at 11–13 weeks[22] in all cases of fetal NT ≥ 99th percentile for crown–rump length (CRL) and at 20 weeks in those with NT between the 95th and 99th percentiles, or tricuspid regurgitation or reversed a-wave in the ductus venosus at 11–13 weeks.

Outcome measures

In this study, we compared measurements of fetal NT and blood flow across the tricuspid valve and ductus venosus at 11–13 weeks in pregnancies with a major fetal heart defect and those resulting in live birth of a morphologically normal baby. Heart defects were considered to be major if they required surgery or interventional cardiac catheterization within the first year postpartum. We included all cases with a major heart defect diagnosed by a pediatric cardiologist antenatally and/or in the neonatal period. Abnormalities suspected antenatally but not confirmed in the neonate were not included. In contrast, the prenatal diagnosis in cases of termination or miscarriage at < 24 weeks or stillbirth at ≥ 24 weeks was assumed to be correct because, in these cases, postmortem examination was not performed systematically. All babies in our hospitals are examined in the neonatal period by a pediatrician, but certain asymptomatic internal abnormalities are inevitably missed. For example, ventricular septal defects or coarctation of the aorta with patent arterial duct may be missed by early neonatal examination, which does not include echocardiography. However, all children with a heart defect diagnosed prenatally or postnatally from our area are examined in a regional pediatric cardiac center which notifies us of any such abnormalities.

We excluded, first, all aneuploidies and non-cardiac defects diagnosed prenatally or in the neonatal period, second, pregnancies with no abnormal fetal findings at the first-, second- or third-trimester scan which resulted in termination, miscarriage or stillbirth and, third, those lost to follow-up. We also excluded the following heart defects: first, ventricular septal defects because they are generally not considered to be major defects; second, right aortic arch, persistent left superior vena cava and aberrant right subclavian artery because these are variants of normal rather than true defects; and, third, cardiac tumors, ventricular aneurysm, arrhythmias and cardiomyopathy, which develop during the second and third trimesters of pregnancy, because these defects would not be expected to have any manifestations at the 11–13-week scan.

Cases with coarctation of the aorta, aortic arch hypoplasia and interrupted aortic arch were classified as arch abnormalities. Similarly, cases with Ebstein's anomaly or tricuspid dysplasia were classified as tricuspid valve abnormalities. Cases with at least two different major heart defects were classified as complex.

Association of major heart defects with increased NT, tricuspid regurgitation and abnormal ductus venosus flow

The incidence of fetal NT ≥ 95th and ≥ 99th percentiles, tricuspid regurgitation and reversed a-wave in the ductus venosus in fetuses with and those without a major heart defect was determined, and the performance of each marker and their combination in the detection of major heart defects was calculated.

Literature search

We searched MEDLINE, EMBASE and the Cochrane Library from inception to October 2019 to identify first-trimester screening studies for major heart defects by increased NT, tricuspid regurgitation or abnormal flow in the ductus venosus. We selected studies involving a minimum of 1000 pregnancies which reported data allowing calculation of detection rate (DR) and false-positive rate (FPR). The results of these studies were tabulated for comparison with our findings.

RESULTS

Study population

During the study period, we carried out an ultrasound examination at 11–13 weeks in 101 793 singleton pregnancies with a live fetus and CRL of 45–84 mm. We excluded 4802 that were lost to follow-up, 796 with a prenatal or postnatal diagnosis of aneuploidy,

1328 with a prenatal or postnatal diagnosis of a non-cardiac defect, 181 with a heart defect that did not meet the inclusion criteria and 1477 with no detectable abnormality but subsequent termination, miscarriage or stillbirth (Figure 1). The study population of 93 209 pregnancies included 211 (0.23%) with a fetal major heart defect and 92 998 morphologically normal neonates.

At the time of the first-trimester scan, median (interquartile range) maternal age of the study population was 31.0 (26.7–34.8) years, maternal weight was 67.3 (59.5–78.5) kg, fetal CRL was 63.8 (58.5–69.6) mm and gestational age was 12.7 (12.3–13.2) weeks; the scan was carried out during the 11th week in only 7853 (8.4%) cases. The racial origin of the women was white in 69 529 (74.6%) cases, black in 15 021 (16.1%), South Asian in 4220 (4.5%), East Asian in 1948 (2.1%) and mixed in 2491 (2.7%). The 11–13-week scan was carried out by one of 476 sonographers.

Major heart defects

In 113 (53.6%) cases with a major heart defect, the diagnosis was made or suspected at the 11–13-week scan, in 82 (38.9%) at the 18–24-week scan, in 10 (4.7%) at the third-trimester scan and in six (2.8%) postnatally. At the 11–13-week scan, we diagnosed all cases of tricuspid or pulmonary atresia and polyvalvular dysplasia, > 90% of cases of hypoplastic left heart syndrome or atrioventricular septal defect, about 60% of complex heart defects and cases of left atrial isomerism (interrupted inferior vena cava with normal intracardiac anatomy), 30–40% of cases of tetralogy of Fallot and arch abnormalities, 25% of tricuspid valve abnormalities and about 15% of cases of transposition of the great arteries, but none of aortic or pulmonary stenosis or common arterial trunk. If a cardiac defect was suspected at the 11–13-week scan but the cardiologist was uncertain of the diagnosis, the patient was reviewed at 15–16 weeks' gestation.

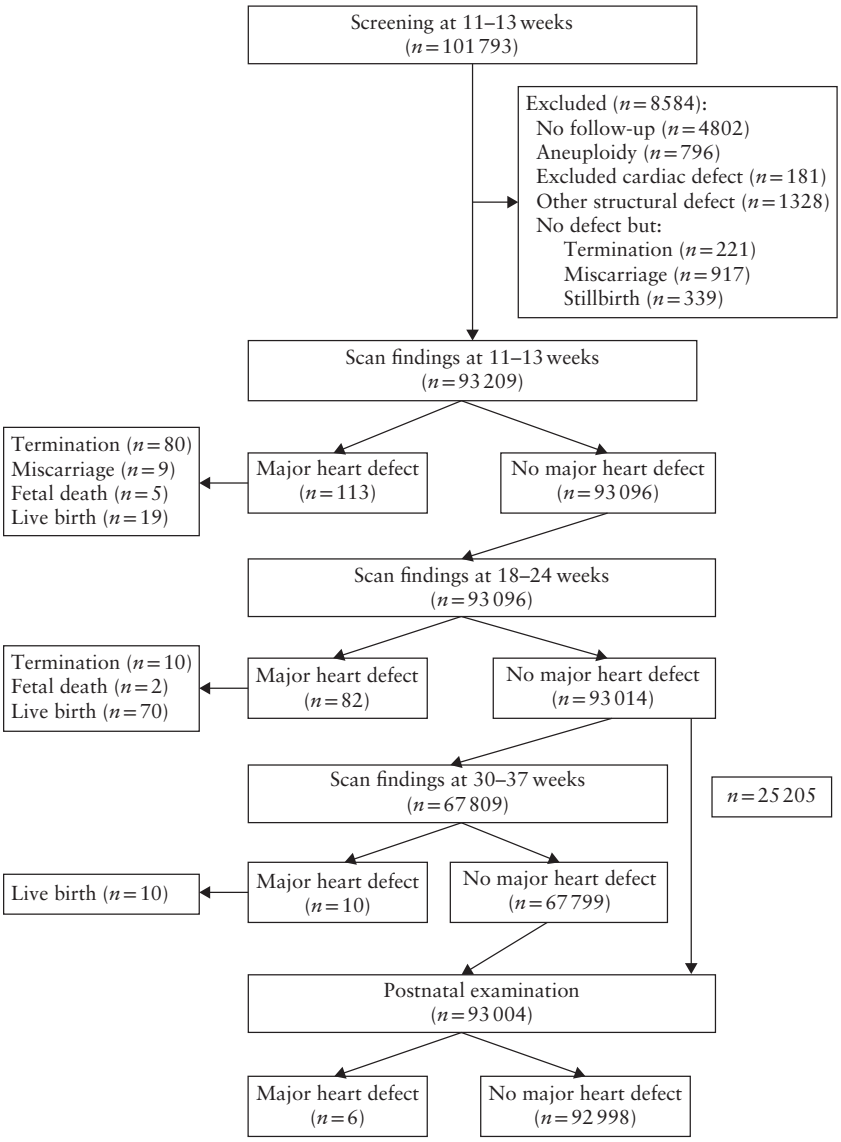

Figure 1 Flowchart summarizing diagnosis of major heart defects in study population.

Association of major heart defects with increased NT, tricuspid regurgitation and abnormal ductus venosus flow

The incidence of increased NT, tricuspid regurgitation and abnormal flow in the ductus venosus was significantly higher in fetuses with than in those without a major heart abnormality (Table 1). The performance of increased NT, tricuspid regurgitation, abnormal flow in the ductus venosus and their combination in the detection of major heart defects is shown in Table 2. Fetal NT $\geq 95^{th}$ or $\geq 99^{th}$ percentile, tricuspid regurgitation or abnormal ductus venosus flow was observed in 77 (36.5%), 45 (21.3%), 61 (28.9%) and 58 (27.5%) of fetuses with a major heart defect, respectively, and in 5678 (6.1%), 857 (0.9%), 1136 (1.2%) and 1644 (1.8%) of those without a heart defect. Any one of NT $\geq 95^{th}$ percentile, tricuspid regurgitation or abnormal flow in the ductus venosus was found in 117 (55.5%; 95% CI, 48.5–62.3%) fetuses with a heart defect and in 8166 (8.8%; 95% CI, 8.6–9.0%)

Table 1 Timing of diagnosis of major heart defects and their association with increased nuchal translucency thickness (NT), tricuspid regurgitation (TR) and abnormal flow in ductus venosus (DV) at 11–13-week scan

		Timing of diagnosis				*Increased NT*				
Group	*Cases* (n)	*First trimester*	*Second trimester*	*Third trimester*	*Postnatal*	*≥ 95th percentile*	*≥ 99th percentile*	*TR*	*Abnormal DV flow*	*Any marker*
Major heart defect	211	113 (53.6)	82 (38.9)	10 (4.7)	6 (2.8)	77 (36.5)	45 (21.3)	61 (28.9)	58 (27.5)	117 (55.5)
Tricuspid atresia	7	7 (100)	0 (0)	0 (0)	0 (0)	3 (42.9)	1 (14.3)	0 (0)	4 (57.1)	4 (57.1)
Pulmonary atresia	11	11 (100)	0 (0)	0 (0)	0 (0)	4 (36.4)	4 (36.4)	6 (54.5)	3 (27.3)	7 (63.6)
Polyvalvular dysplasia	1	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
HLHS	40	37 (92.5)	3 (7.5)	0 (0)	0 (0)	17 (42.5)	9 (22.5)	16 (40.0)	15 (37.5)	25 (62.5)
AVSD	11	10 (90.9)	1 (9.1)	0 (0)	0 (0)	8 (72.7)	7 (63.6)	9 (81.8)	5 (45.5)	10 (90.9)
Complex heart defect	26	16 (61.5)	10 (38.5)	0 (0)	0 (0)	11 (42.3)	6 (23.1)	10 (38.5)	13 (50.0)	18 (69.2)
Left atrial isomerism	7	4 (57.1)	3 (42.9)	0 (0)	0 (0)	3 (42.9)	2 (28.6)	1 (14.3)	2 (28.6)	4 (57.1)
Tetralogy of Fallot	29	11 (37.9)	16 (55.2)	1 (3.4)	1 (3.4)	5 (17.2)	4 (13.8)	7 (24.1)	4 (13.8)	12 (41.4)
Arch abnormality	38	12 (31.6)	21 (55.3)	4 (10.5)	1 (2.6)	18 (47.4)	9 (23.7)	5 (13.2)	8 (21.1)	22 (57.9)
Tricuspid valve abnormality	8	2 (25.0)	3 (37.5)	2 (25.0)	1 (12.5)	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	5 (62.5)
TGA	15	2 (13.3)	12 (80.0)	0 (0)	1 (6.7)	2 (13.3)	0 (0)	1 (6.7)	0 (0)	3 (20.0)
Aortic stenosis	6	0 (0)	4 (66.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	4 (66.7)
Pulmonary stenosis	11	0 (0)	8 (72.7)	2 (18.2)	1 (9.1)	2 (18.2)	0 (0)	0 (0)	0 (0)	2 (18.2)
Common arterial trunk	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Normal live birth	92 998	—	—	—	—	5678 (6.1)	857 (0.9)	1136 (1.2)	1644 (1.8)	8166 (8.8)

Data are given as *n* (%), unless stated otherwise. AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; TGA, transposition of great arteries.

Table 2 Performance of increased nuchal translucency thickness (NT), tricuspid regurgitation (TR), abnormal flow in ductus venosus (DV) and their combination in detection of major heart defect at 11–13-week scan (211 with and 92 998 without major heart defect)

Screening method	*DR*	*FPR*	*LR+*	*LR−*	*PPV (%)*	*NPV (%)*
NT $\geq 95^{th}$ percentile	77; 36.5 (30.0–43.4)	5678; 6.1 (6.0–6.3)	5.98 (4.99–7.15)	0.68 (0.61–0.75)	1.34 (1.12–1.60)	99.85 (99.83–99.86)
NT $\geq 99^{th}$ percentile	45; 21.3 (16.0–27.5)	857; 0.92 (0.86–0.98)	23.14 (17.71–30.24)	0.79 (0.74–0.85)	4.99 (3.86–6.42)	99.82 (99.81–99.83)
TR	61; 28.9 (22.9–35.5)	1136; 1.2 (1.2–1.3)	23.67 (19.01–29.47)	0.72 (0.66–0.78)	5.10 (4.13–6.27)	99.84 (99.82–99.85)
Abnormal DV flow	58; 27.5 (21.6–34.0)	1644; 1.8 (1.7–1.9)	15.55 (12.42–19.46)	0.74 (0.68–0.80)	3.41 (2.74–4.23)	99.83 (99.82–99.85)
NT $\geq 95^{th}$ percentile and/or:						
TR	104; 49.3 (42.4–56.2)	6665; 7.2 (7.0–7.3)	6.88 (5.99–7.90)	0.55 (0.48–0.62)	1.54 (1.34–1.76)	99.88 (99.86–99.89)
Abnormal DV flow	97; 46.0 (39.1–53.0)	7208; 7.8 (7.6–7.9)	5.93 (5.12–6.88)	0.59 (0.52–0.66)	1.33 (1.15–1.54)	99.87 (99.85–99.88)
TR and/or abnormal DV flow	117; 55.5 (48.5–62.3)	8166; 8.8 (8.6–9.0)	6.31 (5.59–7.14)	0.49 (0.42–0.57)	1.41 (1.25–1.59)	99.89 (99.87–99.90)
NT $\geq 99^{th}$ percentile and/or:						
TR	80; 37.9 (31.3–44.8)	1949; 2.1 (2.0–2.2)	18.1 (15.1–21.6)	0.63 (0.57–0.70)	3.94 (3.32–4.68)	99.86 (99.84–99.87)
Abnormal DV flow	73; 34.6 (28.2–41.4)	2460; 2.6 (2.6–2.8)	13.1 (10.8–15.8)	0.67 (0.61–0.74)	2.88 (2.40–3.46)	99.85 (99.83–99.86)
TR and/or abnormal DV flow	99; 46.9 (40.0–53.9)	3517; 3.8 (3.7–3.9)	12.4 (10.7–14.4)	0.55 (0.49–0.63)	2.74 (2.37–3.16)	99.87 (99.86–99.89)

Data are given as *n*; % (95% CI) or with (95% CI). DR, detection rate; FPR, false-positive rate; LR+/−, positive/negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

of those without a heart defect. Any one of NT $\geq 99^{th}$ percentile or the other two markers was found in 99 (46.9%; 95% CI, 40.0–53.9%) fetuses with a heart defect and in 3517 (3.8%; 95% CI, 3.7–3.9%) of those without a heart defect.

Literature search

The findings of screening studies with a minimum of 1000 patients providing data on the association between major heart defect and increased NT, abnormal flow in the ductus venosus and tricuspid regurgitation identified by the literature search are summarized in Table 3.

DISCUSSION

Main findings

This study of 93 209 pregnancies, including 211 (0.23%) with a major heart defect, has demonstrated that: first, > 90% of defects were detected at the first- or second-trimester scan and, in more than half, the diagnosis was made at the 11–13-week scan; second, at the first-trimester scan, all cases of tricuspid or pulmonary atresia and polyvalvular dysplasia, > 90% of cases of hypoplastic left heart syndrome or atrioventricular septal defect, about 60% of complex heart defects and cases of left atrial isomerism (interrupted inferior vena cava with normal intracardiac anatomy), 30–40% of cases of tetralogy of Fallot and arch abnormalities, 25% of tricuspid valve abnormalities and about 15% of cases of transposition of the great arteries, but none of aortic or pulmonary stenosis and common arterial trunk were diagnosed; and, third, any one of NT $\geq 95^{th}$ percentile, tricuspid regurgitation or reversed a-wave in the ductus venosus was found in 55.5% of fetuses with a heart defect and in 8.8% of those without a heart defect, and any one of NT $\geq 99^{th}$ percentile or the other two markers was found in 46.9% of fetuses with a heart defect and in 3.8% of those without a heart defect.

Comparison with findings from previous studies

Our findings in this series of 93 209 pregnancies, examined between 2009 and 2018, are consistent with those in our previous study of 40 990 pregnancies examined between 2006 and 2009. Previous studies reporting on the association between increased NT and major heart defects varied in the definition of increased NT, which included NT $> 95^{th}$ percentile, $\geq 95^{th}$ percentile, > 2.5 mm or $\geq$ 2.5 mm, and of very increased NT, which included NT $> 99^{th}$ percentile, $\geq 99^{th}$ percentile, > 3.5 mm, $\geq$ 3.5 mm or $\geq$ 2.5 multiples of the median[4,9,11,12,23–34]. Our findings that the DR and FPR of NT $\geq 95^{th}$ percentile were about 37% and 6%, respectively, and that those of NT $\geq 99^{th}$ percentile were 21% and 1%, respectively, are consistent with the results of most previous studies.

Six studies reported on the association between abnormal flow in the ductus venosus, defined as

Table 3 Summary of results from screening studies for major heart defects by increased nuchal translucency thickness (NT), abnormal flow in ductus venosus and tricuspid regurgitation

	Pregnancies	*Heart*	*Increased NT*			*Very increased NT*			*Abnormal ductus venosus flow*			*Tricuspid regurgitation*		
Study	(n)	*defect*	*Definition*	*DR*	*FPR*	*Definition*	*DR*	*FPR*	*Definition*	*DR*	*FPR*	*DR*	*FPR*
Hyett (1999)[4]	29 154	50 (0.17)	> 95th percentile	28 (56.0)	1794 (6.2)	> 99th percentile	20 (40.0)	295 (1.0)	—	—	—	—	—
Martinez (2010)[9]	6120	45 (0.74)	—	—	—	> 99th percentile	13 (28.9)	63 (1.0)	A/R a-wave	11 (24.4)	134 (2.2)	—	—
Pereira (2011)[11]	40 990	85 (0.21)	> 95th percentile	30 (35.3)	1956 (4.8)	> 99th percentile	18 (21.2)	290 (0.7)	R a-wave	24 (28.2)	856 (2.1)	28 (32.9)	516 (1.3)
Borrell (2013)[12]	12 836	37 (0.28)	> 95th percentile	15 (40.5)	— (5.0)*	> 99th percentile	10 (27.0)	— (1.0)*	A/R a-wave	14 (37.8)	222 (1.7)	—	—
Michailidis (2001)[23]	6606	9 (0.14)	> 95th percentile	4 (44.4)	219 (3.3)	> 99th percentile	3 (33.3)	60 (0.9)	—	—	—	—	—
Mavrides (2001)[24]	7339	25 (0.34)	≥ 2.5 mm	4 (16.0)	254 (3.5)	≥ 3.5 mm	3 (12.0)	57 (0.8)	—	—	—	—	—
Hafner (2003)[25]	12 978	25 (0.19)	≥ 95th percentile	5 (20.0)	642 (4.9)	—	—	—	—	—	—	—	—
Bruns (2006)[26]	3664	9 (0.25)	> 2.5 mm	2 (22.2)	154 (4.2)	> 3.5 mm	2 (22.2)	31 (0.8)	—	—	—	—	—
Westin (2006)[27]	16 383	55 (0.34)	≥ 95th percentile	8 (14.5)	426 (2.6)	≥ 3.5 mm	3 (5.5)	49 (0.3)	—	—	—	—	—
Muller (2007)[28]	4144	13 (0.31)	> 95th percentile	2 (15.4)	98 (2.4)	> 99th percentile	2 (15.4)	19 (0.5)	—	—	—	—	—
Simpson (2007)[29]	34 266	52 (0.15)	—	—	—	≥ 2.5 MoM	7 (13.5)	202 (0.6)	—	—	—	—	—
Sananes (2010)[30]	12 910	44 (0.34)	≥ 95th percentile	24 (54.5)	1106 (8.6)	≥ 3.5 mm	— (27.3)*	— (1.7)*	—	—	—	—	—
Alanen (2019)[31]	31 144	62 (0.2)	> 95th percentile	26 (41.9)	1531 (4.9)	> 99th percentile	12 (19.4)	299 (1.0)	—	—	—	—	—
Toyama (2004)[32]	1066	5 (0.47)	> 95th percentile	2 (40.0)	134 (12.6)	—	—	—	A/R a-wave	1 (20.0)	59 (5.5)	—	—
Wiechec (2016)[33]	5673	28 (0.49)	—	—	—	—	—	—	R a-wave	6 (21.4)	135 (2.4)	—	—
Volpe (2011)[34]	4445	18 (0.40)	> 95th percentile	7 (38.9)	248 (5.6)	> 99th percentile	4 (22.2)	49 (1.1)	R a-wave	4 (22.2)	137 (3.1)	6 (33.3)	75 (1.7)
Current study	93 209	211 (0.23)	≥ 95th percentile	77 (36.5)	5678 (6.1)	≥ 99th percentile	45 (21.3)	857 (0.9)	R a-wave	58 (27.5)	1644 (1.8)	61 (28.9)	1136 (1.2)

Data are given as *n* (%), unless stated otherwise. Only first author of each study is given. **n*-value not provided in study. A, absent; DR, detection rate; FPR, false-positive rate; MoM, multiples of the median; R, reversed.

reversed or absent/reversed a-wave, and major heart defects[9,11,12,32–34]. The number of pregnancies examined varied from 1066 to 40 990, the incidence of heart defects varied from 0.21% to 0.74%, the DR varied from 20% to 39% and the FPR varied from 1.7% to 5.5%. Our finding of a DR of about 28% at a FPR of 1.8% are consistent with the results of most of these studies.

Two studies reported on the association between tricuspid regurgitation and major heart defects. Pereira *et al.* examined 40 990 pregnancies, including 85 (0.21%) with a major heart defect, and reported that the DR and FPR of tricuspid regurgitation were 32.9% and 1.3%, respectively; the combination of NT $> 95^{th}$ percentile, tricuspid regurgitation or abnormal ductus venosus flow had a DR of 57.6% and FPR of 8.0%[11]. Very similar results were obtained by Volpe *et al.*, who examined 4445 pregnancies, including 18 (0.40%) with a major heart defect, and reported that the DR and FPR of tricuspid regurgitation were 33.3% and 1.7%, respectively; the combination of NT $> 95^{th}$ percentile, tricuspid regurgitation or abnormal ductus venosus flow had a DR of 55.6% and FPR of 10.1%[34].

Implications for clinical practice

Assessment of blood flow across the tricuspid valve and in the ductus venosus was initially incorporated into the 11–13-week scan with the aim of improving the performance of screening for fetal trisomy, especially in women with an intermediate risk on the combined test[35–38]. A secondary benefit arose from the finding of an association between these markers and major heart defects. Recently, the importance of these Doppler studies in screening for trisomy was diminished after the widespread uptake of cell-free DNA testing of maternal blood, especially in women with an intermediate risk on the combined test. However, our findings highlight the continuing importance of these markers in screening for heart defects; increased NT was observed in about 37% of fetuses with a major heart defect, and any one of the three markers was present in 56% of affected fetuses.

In our study, three factors contributed to the high first- and/or second-trimester prenatal detection rate of major heart defects: first, specific training of all sonographers and expectation that they would follow a protocol which includes examination of the transverse section of the thorax and use of color Doppler to assess the four-chamber view of the heart and outflow tracts; second, assessment of blood flow across the tricuspid valve and in the ductus venosus; and, third, ready availability of fetal cardiologists to examine all cases of suspected heart defect and those with increased NT, tricuspid regurgitation or abnormal flow in the ductus venosus. Within such a framework, it is not possible to define the differential contribution of each marker or component of the service in the detection of major heart defects. In cases with optimal examination of the four-chamber view of the heart and outflow tracts, it is unlikely that there would be additional benefit from assessment of tricuspid or ductus venosus flow; however, it is often not possible to achieve such optimal examination and, in such cases, the finding of tricuspid regurgitation or reversed a-wave in the ductus venosus would alert the sonographer to the necessity for referral to a specialist echocardiographer. This is analogous to the second-trimester assessment of the fetal skull and cerebellum for the lemon and banana signs, respectively, or first-trimester intracerebral translucency, which provide clues to the sonographer for the possible need for more careful examination of the spine for diagnosis of open spina bifida[39–43].

Strengths and limitations

The main strength of our study is the examination of a large number of pregnancies attending for routine assessment in the first, second and third trimesters of pregnancy, using standardized protocols and appropriately trained sonographers in units with expertise in fetal medicine and fetal cardiology.

There are three main limitations of this study. First, it was retrospective and recruitment spanned over a 10-year period during which there have been considerable improvements in the quality and resolution of ultrasound imaging. A second limitation of this and most previous studies investigating the effectiveness of routine ultrasound examination in the prenatal diagnosis of major heart defects relates to ascertainment of such abnormalities. Although in our centers all neonates are examined by pediatricians, it is possible that asymptomatic abnormalities, such as coarctation of the aorta with patent arterial duct may be missed by early neonatal examination. A third limitation of this study is the method of diagnosing or excluding a cardiac defect in cases of pregnancy termination or fetal death. We selected the pragmatic endpoint of a defect detectable sonographically by a pediatric cardiologist with expertise in fetal echocardiography. Ideally, in these cases, the antenatal findings should have been validated by postmortem examination.

Conclusions

At 11–13 weeks' gestation, measurement of NT and assessment of flow across the tricuspid valve and in the ductus venosus can lead to early diagnosis of a major heart defect.

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