# Routine ultrasound examination at 12 or 18 gestational weeks for prenatal detection of major congenital heart malformations? A randomised controlled trial comprising 36 299 fetuses

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# Routine ultrasound examination at 12 or 18 gestational weeks for prenatal detection of major congenital heart malformations? A randomised controlled trial comprising 36 299 fetuses

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**Objective** To compare the rate of prenatal diagnosis of heart malformations between two policies of screening for heart malformations.

**Design** Randomised controlled trial.

**Setting** Six university hospitals, two district general hospitals.

**Sample** A total of 39 572 unselected pregnancies randomised to either policy.

**Methods** The 12-week policy implied one routine scan at 12 weeks including measurement of nuchal translucency (NT), and the 18-week policy implied one routine scan at 18 weeks. Fetal anatomy was scrutinised using the same check-list in both groups, and in both groups, indications for fetal echocardiography were ultrasound findings of any fetal anomaly, including abnormal four-chamber view, or other risk factors for heart malformation. In the 12-week scan group, NT ≥3.5 mm was also an indication for fetal echocardiography.

**Main outcome measure** Prenatal diagnosis of major congenital heart malformation.

**Results** In the 12-week scan group, 7 (11%) of 61 major heart malformations were prenatally diagnosed versus 9 (15%) of 60 in the 18-week scan group ($P = 0.60$). In four (6.6%) women in the 12-week scan group, the routine scan was the starting point for investigations resulting in a prenatal diagnosis versus in 9 (15%) women in the 18-week scan group ($P = 0.15$). The diagnosis was made ≤22 weeks in 5% (3/61) of the cases in the 12-week scan group versus in 15% (9/60) in the 18-week scan group ($P = 0.08$).

**Conclusions** The prenatal detection rate of major heart malformations was low with both policies. The 18-week scan policy seemed to be superior to the 12-week scan policy, although the differences in prenatal detection rates were not statistically significant.

**Keywords** Congenital cardiac defect, nuchal translucency measurement, prenatal diagnosis, screening, ultrasonography.

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## Introduction

Cardiac malformations are among the most common congenital abnormalities. The prevalence of heart malformations is estimated to be 8 per 1000 live births, half of those (4 per 1000 live births) being regarded as major, i.e. either lethal or requiring intervention within the first year of life.[1–4] The spectrum of heart defects diagnosed prenatally differs from what is usually seen in postnatal practice. Cardiac malformations diagnosed prenatally are more often complex, i.e. they consist of several separate anatomical defects, and they are often associated with extracardiac malformations and/or abnormal karyotype.[5]

Prenatal diagnosis allows optimisation of perinatal management, i.e. preparation of the parents for the likely outcome and planning of time, mode and site of delivery. The possibility to plan optimal management may improve neonatal outcome, e.g. in case of hypoplastic left heart syndrome, complete transposition of the great arteries or coarctation of the

 

aorta.[6–8] Alternatively, prenatal diagnosis may constitute a rationale for termination of pregnancy.

Results from prospective studies show that the detection rate of major heart defects at routine ultrasound examination at 18–23 gestational weeks in unselected or low-risk populations varies from 0 to 81%.[9–19] In a national survey from the UK including 4000 cases of major cardiac defects, the antenatal detection rate was 23%.[20] This survey is retrospective and does not distinguish between detection at routine and indicated scans. In a study comprising 29 154 euploid fetuses of which 50 had a major congenital heart malformation, Hyett *et al.*[21] investigated first trimester nuchal translucency (NT) measurement as a screening tool for major congenital heart malformation. The use of NT thickness ≥95th percentile to indicate major congenital heart malformation was associated with a sensitivity of 56% (95% CI, 41–70%) and a false-positive rate of 6%, and the use of NT thickness ≥99th percentile (approximately 3.5 mm[22]) with a detection rate of 40% (95% CI, 26–54%) and a false-positive rate of 1%. Hyett *et al.*[21] concluded that 'measurement of fetal NT thickness at 10–14 weeks of gestation is a sensitive method of screening for major defects of the heart and great arteries' and that 'this method of screening compares favourably with using the four-chamber view of the heart at 16–22 weeks of gestation.'

The aim of this study, which was performed in pregnancies derived from the Swedish NUPP trial,[23] was to compare the rate of prenatal diagnosis of congenital heart malformations between two policies of offering prenatal diagnosis: one routine ultrasound examination at 12–14 weeks including NT measurement versus one routine ultrasound examination at 18 weeks.

## Methods

### Study design

The Swedish NUPP trial (NackUPPklarning means nuchal translucency) is a randomised, controlled, national multicentre trial involving eight Swedish hospitals. It includes 39 572 pregnancies and has been described elsewhere according to the CONSORT.[23] It was approved by the Ethics Committees at the Karolinska Institute in Stockholm and those of the Medical Faculties of Lund University and Uppsala University. Women were recruited to the trial between March 1999 and December 2002 from an unselected population of pregnant women cared for at maternity care units affiliated to the hospitals involved. Those who consented to take part were randomised to one of the two policies of offering prenatal diagnosis. The main outcome measure of the NUPP trial was the number of babies born with Down syndrome. Power calculation is described below. The 12-week policy implied one routine scan at 12 weeks including measurement of NT, and the 18-week policy implied one routine scan at 18 weeks. In this study, we compare the rate of prenatal diagnosis of heart malformation between the two policies. Fetal anatomy was scrutinised using the same check-list in both the scan groups, and in both groups, indications for fetal echocardiography were ultrasound findings of any fetal anomaly—including abnormal four-chamber view of the heart—or other risk factors for heart malformation, e.g. family history. The 12-week policy also included NT ≥3.5 mm as an indication for fetal echocardiography. Fetal echocardiography was carried out by an obstetrician or paediatric cardiologist specially trained in fetal echocardiography. Details of each policy are given below. Details about the ultrasound operators and equipment are described elsewhere.[23]

### Details of the 12- to 14-week scan policy

The 12-week scan included fetal biometry, scrutiny of the fetal anatomy, measurement of NT and calculation of risk of trisomy 21 using the software developed by the Fetal Medicine Foundation (FMF).[24] Anatomy screening was performed following the same check-list as in the 18-week scan group. However, in the 12-week scan group, inadequate visualisation of the four-chamber view of the heart was accepted provided that NT was within the normal range. Women at increased risk of fetal aneuploidy according to NT screening who declined fetal karyotyping or whose fetuses proved to have normal chromosomes were offered a re-scan of the fetal anatomy at 18 weeks by one of the obstetricians involved in the trial. Fetal echocardiography was offered to women whose fetus had NT ≥3.5 mm if fetal chromosomes were normal or if the woman declined fetal karyotyping, and at one centre (contributing 1257 of the 18 148 pregnancies in the 12-week scan group), fetal echocardiography was also offered to women with risk of trisomy 21 ≥1:250 if fetal chromosomes were normal or the woman declined fetal karyotyping.

### Details of the 18-week scan policy

Fetal anatomy was scrutinised following the same check-list as in the 12-week scan group. Visualisation of the four-chamber view of the heart was obligatory. Examination of the outflow tracts of the heart did not form part of the standard 18-week examination. If the four-chamber view was abnormal or difficult to interpret, the woman was referred to a scan by an obstetrician, who then, if indicated, referred her for fetal echocardiography.

### Follow up

To facilitate follow up, all women were given a questionnaire at their routine scan where they were asked to report pregnancy outcome. Information on pregnancy outcome was retrieved from delivery records; from departments of neonatology, paediatric cardiology, genetics and pathology providing services to the hospitals involved and from the National Registry of Congenital Anomalies. Newborns were followed up with regard to heart malformation until 12 months of age. All

information about the pregnancies in the trial, the results of the ultrasound examinations and outcome of pregnancy was collected in an internet-based anonymous database.

### Outcome variables, classification of cardiac defects

Congenital cardiac defects were subdivided into major and minor malformations by the paediatric cardiologist of our team (G.B.). A major heart malformation was defined as one requiring surgery or catheter intervention—except interventions for persisting arterial duct or atrial septal defect (ASD) secundum—within the first 12 months of life. In addition, a ventricular septal defect (VSD) was regarded as a major cardiac malformation if the child was symptomatic, despite pharmacological treatment. For consistency and to facilitate comparison of our results with those of others, cardiac defects were grouped into eight categories modified after Makrydimas *et al.*[25]

1. Left heart lesions (including hypoplastic left heart syndrome, aortic atresia with or without mitral atresia, aortic valve stenosis and coarctation of the aorta with or without VSD).
2. Right heart lesions (including tricuspid atresia, tricuspid valve dysplasia, Ebstein's anomaly, pulmonary atresia with or without VSD and pulmonary stenosis).
3. Septal defects (including ASD and VSD, and atrioventricular septal defects with normal situs).
4. Outflow tract anomalies (including transposition of the great arteries with or without VSD, common arterial trunk, tetralogy of Fallot with or without atresia of the pulmonary valve and absent pulmonary valve syndrome).
5. Laterality anomalies (including left and right atrial isomerism).
6. Complex abnormalities (including atrioventricular to ventriculoatrial disconcordance, double outlet right ventricle and double inlet ventricle).
7. Other lesions (e.g. cardiomyopathy, abnormal pulmonary venous drainage).
8. Nonclassifiable cases.

### Statistical analysis

The prevalence of congenital heart malformations and the rate of prenatal diagnosis of congenital heart malformations were compared between the 12-week scan group and the 18-week scan group. All statistical analyses were carried out using the Statistical Package for the Social Sciences (2003; SPSS Inc., Chicago, IL, USA). The statistical significance of differences in proportions was determined using Fisher's exact test or the chi-square test. A two-sided $P$ value $<0.05$ was considered statistically significant.

The sample size in the NUPP trial (18 000 women in each group) was calculated to give the trial power to show a change in the number of babies born with Down syndrome. Details on our power calculation have been published.[23] The power of the trial to detect possible differences in detection rates of heart malformations is low. Assuming a detection rate of 23% (mean detection rate in a national survey from the UK[20]) and a prevalence of major heart malformations of 0.4%,[1–4] and using an alpha error (two sided) of 0.05 and a power of 0.80, a sample size of 62 750 fetuses in each arm of a trial would be needed to detect a 10% (absolute value) difference in prenatal detection rate as statistically significant. Our actual sample size of approximately 18 150 fetuses in each arm would allow detection of a change in detection rate from 23 to 33% with a power of 0.17 or from 23 to 13% with a power of 0.22, and a change from 15 to 5% with a power of 0.33 or from 15 to 25% with a power of 0.20.

## Results

Of 39 572 women randomised, 36 240 turned up for their routine scan. All fetuses alive at the routine scan are included in our analysis irrespective of whether they were later found to have a chromosomal abnormality.

In the 12-week scan group, 18 266 fetuses were alive at the scan, 118 were lost to follow up and 18 148 were included. Of the 18 148 living fetuses included in the 12-week scan group, 16 567 had an NT measurement. Absent information on NT in 1699 fetuses is explained by the woman being too advanced in her pregnancy for NT measurement to be possible (crown rump length >84 mm), difficulties with obtaining an accurate measurement, failure to enter the result of the NT measurement into the trial database and, in a few cases, obvious lethal fetal malformations, e.g. anencephaly. The four-chamber view was properly seen in 10 274 fetuses, judged as suspicious in 16 fetuses and not possible to evaluate in 7858 fetuses. In the 18-week scan group, 18 288 fetuses were alive at the scan, 137 were lost to follow up and 18 151 were included. Of the 18 151 fetuses in the 18-week scan group, 19 had a suspicious four-chamber view, six of which had a major heart malformation.

Among the 36 299 fetuses included, we identified 294 fetuses with a congenital heart malformation (8.1/1000), of which 121 fetuses had a major heart malformation (3.3/1000). Both the total prevalence of congenital heart defects and the prevalence of major heart defects were almost identical in the 12-week scan group and the 18-week scan group (139/18 148 versus 155/18 151, i.e. 7.7/1000 versus 8.5/1000; 61/18 148 versus 60/18 151, i.e. 3.4/1000 versus 3.3/1000). The cardiac malformations are described in Table 1. The outcome of fetuses affected by a heart malformation is presented in Table 2.

In the 12-week scan group, 7 of the 61 cases of major heart malformation were prenatally diagnosed (11%, 95% CI 4.7–22.2) versus 9 of the 60 cases (15%, 95% CI 7.1–26.6) in the 18-week scan group ($P = 0.60$). In the 12-week scan group, 4 of the 61 cases (6.6%, 95% CI 1.8–16.0) were

**Table 1.** Description of the cardiac malformations

| | 12-week scan group (*n*) | 18-week scan group (*n*) |
|---|---|---|
| **Major malformations** | 61 | 60 |
| Left heart | 11 | 16 |
| Right heart | 13 | 10 |
| Septal defects | 19 | 17 |
| Outflow tract defects | 12 | 13 |
| Laterality defects | 2 | 2 |
| Complex abnormalities | 3 | 2 |
| Other | 1 | 0 |
| **Minor malformations** | | |
| ASD | 8 | 12 |
| VSD | 62 | 76 |
| Nonclassifiable | 8 | 7 |

detected at the routine scan, i.e. the routine scan was the starting point for investigations eventually resulting in a prenatal diagnosis of a major cardiac malformation, and in the 18-week scan group, 9 of the 60 cases (15.0%, 95% CI 7.1–26.6) were detected at the routine scan ($P = 0.15$). In the 12-week scan group, three diagnoses were made before 22 weeks (5%, 95% CI 1.0–14.0) versus nine in the 18-week scan group (15%, 95% CI 7–27; $P = 0.08$).

### Details of the 12-week scan group

Details about the prenatally diagnosed cases of major cardiac malformations in the 12-week scan group are presented in Table 3. Three of the seven cases diagnosed before birth in the 12-week scan group were detected incidentally at a scan performed because of pregnancy complications at ≥28 weeks.

Among the 16 567 fetuses with information on NT thickness, the risk of Down syndrome according to NT screening was ≥1:250 in 587 fetuses (3.5%), and NT was ≥3.5 mm in 77 fetuses (0.5%). Of the 61 fetuses with a major heart malformation, 3 (5%) had NT ≥3.5 mm and 6 (10%) had increased risk of Down syndrome but NT <3.5 mm. None of the three fetuses with a major cardiac malformation and NT ≥3.5 mm had their heart malformation diagnosed before birth: one was not referred for fetal echocardiography by an administrative mistake (preductal coarctation of the aorta diagnosed after birth), one miscarried before fetal echocardiography was performed (common arterial trunk diagnosed at autopsy) and in one fetus an ASD and a VSD were missed at fetal echocardiography but diagnosed after birth. Three of the six fetuses with a major heart malformation and increased risk of Down syndrome but NT <3.5 mm underwent fetal echocardiography: two of them had their heart malformation diagnosed prenatally, but in the third fetus, stenosis of the pulmonary valves was not detected at the fetal echocardiography but diagnosed after birth.

**Table 2.** Outcome of fetuses with congenital cardiac malformation

| | 12-week scan group, *n* = 18 148 | 18-week scan group, *n* = 18 151 | *P* value |
|---|---|---|---|
| **Any heart malformation** | 139 | 155 | |
| **Major heart malformation** | 61 | 60 | |
| Prenatally diagnosed (%) | 7 (11) | 9 (15) | 0.60 |
| Diagnosed ≤22 weeks (%) | 3 (5) | 9 (15) | 0.08 |
| Legal abortion | 3 | 7 | |
| Fetal loss | 1 | 0 | |
| Liveborn | 57 | 53 | |
| Neonatal death | 1 | 0 | |
| Death within 12 months | 2 | 2 | |
| **Minor heart malformation** | 78 | 95 | |
| Prenatally diagnosed (%) | 1 (1) | 0 (0) | |

### Details of the 18-week scan group

Details about the prenatally diagnosed cases of major heart malformation in the 18-week scan group are presented in Table 4. In all nine cases diagnosed before birth, the indication for fetal echocardiography was abnormal fetal anatomy at the routine scan: in eight cases, the heart appeared abnormal, and in one case (Fallot's tetralogy), a finding of gastroschisis was the indication to perform fetal echocardiography.

## Discussion

Our purpose was to compare two complete policies of offering prenatal screening for major heart malformations. We wondered whether it would be possible to replace our current policy of offering one routine scan at 18 weeks with a policy of offering one routine scan at 12 weeks. Because of the high sensitivity of increased NT with regard to heart malformation reported by Hyett *et al.*,[21] we believed that with regard to prenatal diagnosis of heart malformations this would be possible. Where for priority reasons it is possible to offer only one routine scan during pregnancy, it is a clinically important question how to best organise a service of offering prenatal diagnosis to all pregnant women.

Our 18-week policy was associated with a disappointingly low rate of prenatal diagnosis of major cardiac malformations (15%), although our prenatal detection rate fell within the range of detection rates reported in prospective studies conducted in settings that seem to have been similar to ours (0–75%).[9–11,13,14,16–19] The extremely wide variation in reported prenatal detection rates of heart malformations at routine mid-gestation scans (0–81%[9–20,26,27]) is to be explained not only by differences in operator skills but also by differences in

**Table 3.** Major cardiac malformations diagnosed prenatally in the 12-week scan group

| Postnatal diagnosis | Gws at decision to perform fetal echocardiography | Indication for fetal echocardiography | Gws at diagnosis | Genotype | Outcome |
|---|---|---|---|---|---|
| Complex situs inversus, AV discordance | 12 | Dextrocardia at 12-week scan | 18 | Normal | TOP |
| Common arterial trunk | 12 | Risk of trisomy 21, 1:243 (NT 1.7 mm) | 23 | Autosomal monosomy | Alive at 12 months |
| Single ventricle, TGA | 18 | Abnormal kidneys at 12-week scan | 19 | Normal | TOP |
| Hypoplasitc left heart syndrome | 18 | Risk of trisomy 21, 1:123 (NT 2.3 mm) | 19 | Normal | TOP |
| Tetralogy of Fallot | 28 | IUGR | 28 | Normal | Alive at 12 months |
| Double outlet right ventricle, AVSD | 33 | Polyhydramnion | 34 | Normal | Death at 4 days |
| Malformation of tricuspid valve and pulmonary artery | 35 | Cardiac arrhythmia | 35 | Normal | Alive at 12 months |

AV, atrioventricular; AVSD, atrioventricular septal defect; Gws, gestational weeks; IUGR, intrauterine growth restriction; TGA, transposition of the great arteries; TOP, termination of pregnancy.

study design (retrospective[20,26,27] or prospective[9–19]), study population (unselected,[10–16,26,27] low risk[9,17–19] or not clearly described[20]), definition of major heart malformation (complex malformations,[16] malformations potentially detectable by abnormal four-chamber view[12,18] or—as in our present study—all cases requiring surgery or catheter intervention within the first 12 months of life but also VSDs where the child was symptomatic despite pharmacological treatment),

**Table 4.** Major cardiac malformations diagnosed prenatally in the 18-week scan group

| Postnatal diagnosis | Gws at decision to perform fetal echocardiography | Indication for fetal echocardiography | Gws at diagnosis | Genotype | Outcome |
|---|---|---|---|---|---|
| TGA | 15 | Multiple malformations, enlarged heart | 16 | Trisomy 18 | TOP |
| Tetralogy of Fallot | 16 | Extracardiac malformations | 17 | Normal | TOP |
| Double outlet right ventricle, isomerism of the atrias, stenosis of the pulmonary valve | 17 | Abnormal four-chamber view | 19 | Normal | Alive at 12 months |
| Common arterial trunk, dextrocardia | 17 | Abnormal four-chamber view | 17 | Normal | TOP |
| Tetralogy of Fallot, double outlet right ventricle, stenosis of the aorta | 17 | Abnormal four-chamber view | 18 | Normal | Alive at 12 months |
| TGA, AV discordance, functionally one-ventricle heart | 18 | Abnormal outflow tract | 18 | Normal | TOP |
| Ebstein's anomaly | 18 | Abnormal four-chamber view | 20 | Normal | Death at 3 months |
| Hypoplastic left heart syndrome | 18 | Abnormal four-chamber view | 20 | Normal | TOP |
| Common arterial trunk | 20 | Enlarged heart, VSD? | 22 | Normal | Alive at 12 months |

AV, atrioventricular; Gws, gestational weeks; TGA, transposition of the great arteries; TOP, termination of pregnancy.

and the completeness of postnatal follow up. Incomplete follow up results in low prevalence of heart malformations and falsely high detection rate. The high detection rate of 69% reported by Sharland and Allan[12] may be partly explained by them only including major heart malformations potentially detectable by an abnormal four-chamber view. Rustico *et al.*[18], too, excluded some heart malformations that are difficult to detect in the second trimester, e.g. progressive valvular stenosis, but their detection rate was less than half of that reported by Sharland and Allan (31%). Because only about 50% of all heart malformations are supposed to be detectable by an abnormal four-chamber view,[28] the 81% detection rate by Vergani *et al.*,[15] who seem not to have included examination of the outflow tracts in their routine scans, is difficult to explain. Incomplete follow up may have been a source of bias in some studies, where the prevalence of major heart malformation is neither reported nor possible to calculate[12,13,20] or much lower than expected (0.1%).[17,19,26] Our own low prenatal detection rate of congenital heart malformations in the 18-week scan group was associated with a very low rate of abnormal four-chamber view (19 cases, i.e. 0.1%). This low rate of abnormal four-chamber view is identical to that reported by Buskens *et al.*[9] (who had a 17% prenatal detection rate of heart malformations) and Luck[10] (who had a 36% prenatal detection rate of heart malformations) but much lower than the 4% reported by Tegnander *et al.*[11] (who had 26% second trimester detection rate of major heart malformations). However, abnormal four-chamber view seems to have been defined differently in the studies cited. Buskens *et al.*[9] and Vergani *et al.*[15] defined abnormal four-chamber view as a suspicious view, and Tegnander *et al.*[11] included in their definition of abnormal four-chamber view inability to obtain a four-chamber view at the routine scan. It is often not possible to calculate the rate of abnormal four-chamber view on the basis of data presented in articles either because of uncertainty about the total number of women scanned[12,13,20] or because the number of cases with abnormal or uninterpretable four-chamber view is not given.[14,26,27]

Our rate of prenatal diagnosis of heart malformations in the 12-week scan group was even lower than that in the 18-week scan group (5, 7 or 11% depending on how detection rate is defined versus 15%), although the differences were not statistically significant. Lack of statistical significance is almost certainly to be explained by low power. Only 3 (5%) of the 61 fetuses in the 12-week scan group with a major heart malformation had NT ≥3.5 mm, and none of these fetuses had their diagnosis before birth (miscarriage before fetal echocardiography, not referred for fetal echocardiography by an administrative mistake, missed diagnosis of stenosis of the pulmonary valves at fetal echocardiography). Only 0.5% of the fetuses that had an NT measurement documented in our trial versus the expected 1% had NT ≥3.5 mm. This would seem to indicate that our NT measurements were too 'conservative' and could explain the low sensitivity of NT ≥3.5 mm with regard to heart malformation. In contrast, our measurements were regularly checked and approved by the FMF, and others, too, have reported low sensitivity of NT ≥3.5 mm with regard to heart malformation (0[29] and 11%[30]). The use of a lower NT cutoff than 3.5 mm would probably have been associated with a higher sensitivity but also with a larger number of fetuses that would have needed to undergo fetal echocardiography. We chose the 3.5-mm cutoff believing that 1% of our fetuses would need to be referred for fetal echocardiography on the basis of increased NT (in addition to those referred on other indications included in the 12-week policy). Our resources would not have allowed a higher percentage of fetuses to be examined by fetal echocardiography. The size of a test-positive group needing specialist investigation needs to be taken into account when planning routine antenatal care. In the 12-week scan group, two cases (3%) of major heart defects were detected at fetal echocardiography performed because of increased risk of Down syndrome according to NT screening, but both fetuses had NT <3.5 mm. If all fetuses with NT ≥3.5 mm and/or a risk of Down syndrome ≥1:250 according to NT screening would have undergone fetal echocardiography, 9 (15%) of the 61 cases of major heart malformation in the 12-week scan group would have been potentially detectable for a test-positive rate of 3.5%. This hypothetical 15% detection rate is equal to the actual detection rate of the 18-week scan policy. However, using the calculated risk of Down syndrome as a screening tool for heart malformations is questionable because risk calculation is based on history of chromosomal aberrations, maternal age, gestational age and NT. Of these parameters, only increased NT is known to be associated with increased risk of congenital heart malformation.

Because improved prognosis can be expected for babies with some types of heart malformations if the diagnosis is made before birth,[6–8] the low rate of prenatal diagnosis of major heart malformations not only in our study but also in others[9,14,19] is a problem. Pooling results from prospective studies examining the performance of midtrimester routine ultrasound examination in an unselected population undertaken in a setting similar to ours[9–11,13,14,16–19] yielded a detection rate of 36%. It seems that in the prospective studies reporting the highest detection rates,[12,15,16] the skill of those performing the routine scans was higher than that of our operators because in the studies cited, the operators were continuously and systematically taught how to obtain, recognise and interpret the four-chamber view,[12,16] or the operators consisted of a limited number of obstetricians with special training in fetal ultrasonography.[15] Moreover, in the study by Carvalho *et al.*[16], the sonographers were encouraged to include examination of the outflow tracts of the heart in their routine scans. Easy access to fetal echocardiography is also

likely to have contributed to the high rate of prenatal diagnoses in the studies cited.[12,15,16]

Despite the low power of our trial, we believe that our results do not support the idea of replacing the 18-week policy with the 12-week policy as we have defined these policies in our trial. We would rather recommend that resources be spent on teaching and training those performing routine scans in pregnancy to visualise and interpret the four-chamber view of the heart at 18–23 weeks and to include examination of the great vessels into the routine scan. The efficacy of routine ultrasound screening for major congenital heart malformations can be improved by education and training of operators[11,31–33] and by including examination of the outflow tracts of the heart.[31] The time spent learning to obtain a four-chamber view and a proper view of the outflow tracts is relatively long.[32] Systematic training of operators, a low threshold for referring patients for fetal echocardiography and easy access to fetal echocardiography followed by direct feedback to the operator would probably facilitate the building up of the skills of those performing routine scans in pregnancy.

The question of whether adding a 12-week NT scan to an 18-week fetal anatomy scan would increase the prenatal detection rate of major cardiac malformations—while keeping the number of fetuses needing to undergo specialist fetal echocardiography reasonably low—can only be answered in a randomised controlled trial. Assuming a detection rate of 23% and[20] a prevalence of major heart malformations of 0.4%,[1–4] using alpha error (two sided) 0.05 and power 0.80, and defining a 10% difference in detection rate as clinically relevant, a sample size of 62 750 fetuses in each arm of the trial would be needed.

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## Summary

We have compared two policies of offering prenatal diagnosis to all pregnant women with regard to prenatal detection of major heart malformation, i.e. one scan at 12–14 weeks including NT measurement versus one scan at 18–20 weeks, both scans including scrutiny of fetal anatomy. The rate of prenatal diagnosis of heart malformation was low with both policies. The 18-week scan policy seemed to be superior to the 12-week scan policy, although the differences in prenatal detection rates were not statistically significant. The question of whether adding a 12-week NT scan to an 18-week fetal anatomy scan would increase the prenatal detection rate of major cardiac malformations can be answered in a randomised controlled trial including 62 750 fetuses in each arm.

## Steering Committee of NUPP trial

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## Database

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## References

1 Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births: incidence and natural history. *Circulation* 1971; 43:323–32.
2 Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, *et al*. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington infant study. *Am J Epidemiol* 1985;121:31–6.
3 Hoffman JIE. Incidence of congenital heart disease: postnatal incidence. *Pediatr Cardiol* 1995;16:103–13.
4 Campbell M. Incidence of cardiac malformations at birth and later, and neonatal mortality. *Br Heart J* 1973;35:189–200.
5 Allan LD, Sharland GK, Milburn A, Lockhart SM, Groves AM, *et al*. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. *J Am Coll Cardiol* 1994;23:1452–8.
6 Tworetzky W, McElhinney DB, Reddy VM, Brook MM, Hanley FL, Silverman NH. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation* 2001;103:1269–73.
7 Bonnet D, Coltri A, Butera G, Fermont L, Le Bidois J, Kachaner J, *et al*. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. *Circulation* 1999;99:916–18.
8 Franklin O, Burch M, Manning N, Sleeman K, Gould S, Archer N. Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. *Heart* 2002;87:67–9.
9 Buskens E, Grobbee DE, Frohn-Mulder IM, Stewart PA, Juttmann RE, Wladimiroff JW, *et al*. Efficacy of routine fetal ultrasound screening

for congenital heart disease in normal pregnancy. *Circulation* 1996; 94:67–72.
**10** Luck CA. Value of routine ultrasound scanning at 19 weeks: a four-year study of 8849 deliveries. *BMJ* 1992;304:1474–8.
**11** Tegnander E, Eik-Nes SH, Johansen OJ, Linker DT. Prenatal detection of heart defects at the routine fetal examination at 18 weeks in a non-selected population. *Ultrasound Obstet Gynecol* 1995;5:372–80.
**12** Sharland GK, Allan LD. Screening for congenital heart disease prenatally. Results of a 2, 5 year study in the South East Thames Region. *Br J Obstet Gynaecol* 1992;99:220–5.
**13** Grandjean H, Larroque D, Levi S, Eurofetus Study Group. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. *Am J Obstet Gynecol* 1999;181:446–54.
**14** Eurenius K, Axelsson O, Cnattingius S, Eriksson L, Norsted T. Second trimester ultrasound screening performed by midwives; sensitivity for detection of fetal anomalies. *Acta obstet Gynecol Scand* 1999;78:98–104.
**15** Vergani P, Mariani S, Ghidini A, Schiavina R, Cavallone M, Locatelli A, *et al*. Screening for congenital heart disease with the four-chamber view of the fetal heart. *Am J Obstet Gynecol* 1992;167:1000–3.
**16** Carvalho JS, Mavrides E, Shinebourne EA, Campell S, Thilaganathan B. Improving the effectiveness of routine prenatal screening for major congenital heart defects. *Heart* 2002;88:387–91.
**17** Shirley IM, Bottomley F, Robinson VP. Routine radiographer screening for fetal abnormalities by ultrasound in an unselected low-risk population. *Br J Radiol* 1992;65:564–9.
**18** Rustico MA, Benettoni A, D'Ottavio G, Maieron A, Fisher-Tamaro I, Conoscenti G, *et al*. Fetal heart screening in low-risk pregnancies. *Ultrasound Obstet Gynecol* 1995;6:313–19.
**19** Ott WJ. The accuracy of antenatal fetal echocardiography screening in high- and low risk patients. *Am J Obstet Gynecol* 1995;172:1741–7.
**20** Bull C. Current and potential impact of fetal diagnosis on prevalence and spectrum of serious congenital heart disease at term in the UK. British Paediatric Cardiac Association. *Lancet* 1999;354:1242–7.
**21** Hyett J, Perdu M, Sharland G, Snijders R, Nicolaides KH. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *BMJ* 1999; 318:81–5.
**22** Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* 1998; 352:343–6.
**23** Saltvedt S, Almstrom H, Kublickas M, Valentin L, Bottinga R, Bui TH, *et al*. Screening for Down syndrome based on maternal age or fetal nuchal translucency: randomized controlled trial in 39572 pregnancies. *Ultrasound Obstet Gynecol* 2005;25:537–45.
**24** Nicolaides KH, Snijders RJM, Sebire N. The 11–14 week scan: the diagnosis of fetal abnormalities. In: Nickolaides KH. editor. *Diploma in Fetal Medicine Series*, Vol. 2. London: The Parthenon Publishing Group; 1999:3–65.
**25** Makrydimas G, Sotiriadis A, Huggon IC, Simpson J, Sharland G, Carvalho JS, *et al*. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. *Am J Obstet Gynecol* 2005;192:89–95.
**26** Chitty LS, Hunt GH, Moore J, Lobb MO. Effectiveness of routine ultrasonography in detecting fetal structural abnormalities in a low-risk population. *BMJ* 1991;303:1165–9.
**27** Garne E, Stoll C, Clementi M, Euroscan Group. Evaluation of prenatal diagnosis of congenital heart diseases by ultrasound: experience from 20 European registers. *Ultrasound Obstet Gynecol* 2001;17:386–91.
**28** Allen LD, Crawford DC, Anderson RH, Tynan MJ. Spectrum of congenital heart disease detected echocardiographically in prenatal life. *Br Heart J* 1985;54:523–36.
**29** Josefsson A, Molander E, Selbing A. Nuchal translucency as a screening test for chromosomal abnormalities in a routine first trimester ultrasound examination. *Acta Obstet Gynecol Scand* 1998;77:497–9.
**30** Mavrides E, Cobian-Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, *et al*. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart defects. *Ultrasound Obstet Gynecol* 2001;17:106–10.
**31** Tegnander E, William W, Johansen J, Blaas HG, Eik-Nes SH. Prenatal detection of congenital heart defects in a non-selected population of 30 139 fetuses. *Ultrasound Obstet Gynecol* 2006;27:252–65.
**32** Tegnander E, Eik-Nes SH. The examiner's ultrasound experience had a significant impact on the detection rate of congenital heart defects at the second trimester fetal examination. *Ultrasound Obstet Gynecol* 2004;24:217.
**33** Hunter S, Heads J, Wyllie, Robson S. Prenatal diagnosis of congenital heart disease in the northern region of England: benefits of a training programme for obstetric ultrasonographers. *Heart* 2000;84:294–8.