



Effectiveness of 12–13-week scan for early diagnosis of fetal congenital anomalies in the cell-free DNA era

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ABSTRACT

Objectives The main aim of this study was to assess the proportion and type of congenital anomalies, both structural and chromosomal, that can be detected at an early scan performed at 12–13 weeks' gestation, compared with at the 20-week structural anomaly scan offered under the present screening policy. Secondary aims were to evaluate the incidence of false-positive findings and ultrasound markers at both scans, and parental choice regarding termination of pregnancy (TOP).

Methods Sonographers accredited for nuchal translucency (NT) measurement were asked to participate in the study after undergoing additional training to improve their skills in late first-trimester fetal anatomy examination. The early scans were performed according to a structured protocol, in six ultrasound practices and two referral centers in the north-east of The Netherlands. All women opting for the combined test (CT) or with an increased a-priori risk of fetal anomalies were offered a scan at 12–13 weeks' gestation (study group). All women with a continuing pregnancy were offered, as part of the 'usual care', a 20-week anomaly scan.

Results The study group consisted of 5237 women opting for the CT and 297 women with an increased a-priori risk of anomalies (total, 5534). In total, 51 structural and 34 chromosomal anomalies were detected prenatally in the study population, and 18 additional structural anomalies were detected after birth. Overall, 54/85 (63.5%) anomalies were detected at the early scan (23/51 (45.1%) structural and all chromosomal anomalies presenting with either an increased risk at first-trimester screening or structural anomalies (31/34)). All particularly severe anomalies were detected at the early scan (all

cases of neural tube defect, omphalocele, megacystis, and multiple severe congenital and severe skeletal anomalies). NT was increased in 12/23 (52.2%) cases of structural anomaly detected at the early scan. Of the 12 cases of heart defects, four (33.3%) were detected at the early scan, five (41.7%) at the 20-week scan and three (25.0%) after birth. False-positive diagnoses at the early scan and at the 20-week scan occurred in 0.1% and 0.6% of cases, respectively, whereas ultrasound markers were detected in 1.4% and 3.0% of cases, respectively. After first- or second-trimester diagnosis of an anomaly, parents elected TOP in 83.3% and 25.8% of cases, respectively.

Conclusions An early scan performed at 12–13 weeks' gestation by a competent sonographer can detect about half of the prenatally detectable structural anomalies and 100% of those expected to be detected at this stage. Particularly severe anomalies, often causing parents to choose TOP, are amenable to early diagnosis. The early scan is an essential part of modern pregnancy care. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Ten years after the introduction of the Dutch prenatal screening program aimed at increasing the reproductive choices of parents with a diagnosis of fetal anomaly^{1,2}, a marked difference in the uptake of the two screening methods has been noted. The combined test (CT) has an uptake of around 30% and the 20-week scan an uptake of around 95%. The CT is not free of charge and is offered exclusively as a screening test for aneuploidies³. The low uptake is thought to reflect a general mistrust

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in the performance of the test and a high acceptance of Down syndrome (trisomy 21), which is not considered by many parents as a reason to terminate a pregnancy^{3,4}.

Recently, the Dutch Ministry of Health agreed to offer non-invasive whole-genome sequencing (cell-free DNA (cfDNA) testing) to all pregnant women as first-tier screening for trisomies⁵, as an alternative to the CT. This raises the issue as to whether an early scan should also be offered to all pregnant women. Although early scans are performed for dating, location of pregnancy and the diagnosis of multiple pregnancy^{6–8}, there is compelling evidence that diagnosis of structural anomalies is also possible from the late first trimester⁹. It is, therefore, necessary to reappraise the role of an early scan in screening for congenital anomalies¹⁰.

The primary aim of this study was to examine the proportion and type of congenital anomalies, both chromosomal and structural, detected by an early scan (at 12–13 weeks' gestation; new strategy), compared with

the 20-week scan (current strategy). Secondary aims were to evaluate the incidence of false-positive findings and ultrasound markers at both scans, and parental choice regarding termination of pregnancy (TOP).

METHODS

Two referral centers (University Medical Centre in Groningen and Isala Hospital in Zwolle) and six ultrasound practices in the provinces of Groningen and Overijssel participated in the study. Only sonographers accredited for nuchal translucency (NT) measurement and performing at least 100 NT scans per year were eligible to participate in the study.

A special license was obtained for the study from the Ministry of Health, within the Dutch Population Screening Act¹¹, regulating screening for incurable diseases. Women opting for the CT were asked by their referring midwife to participate in the study, and received

Table 1 Protocol followed for early anatomical survey indicating views that should be obtained, structures that should be investigated and measurements that should be taken in order to exclude or detect all anomalies that should be seen at an early scan

<i>Longitudinal view/examined structure [measurement]</i>	<i>Axial/tangential view [measurement]</i>	<i>Anomaly</i>
<i>Head</i>		
Evaluation of skull contour [Nuchal translucency]	Visualization of midline [BPD, HC]	Acrania/anencephaly*
Profile	Symmetry of choroid plexus	Holoprosencephaly (alobar)*
Nasal bone	Visualization of orbits	Exencephaly containing brain tissue*
Intracranial translucency	Retronasal triangle, lips	Micrognathia, cleft lip and palate†
		Micro-anophthalmia†
		Large nuchal translucency/cystic hygroma*
<i>Body</i>		
Diaphragm	Umbilical cord insertion	Large omphalocele*
Stomach (below diaphragm)	Umbilical arteries along bladder	Gastroschisis†
Bladder filling		Diaphragmatic hernia (stomach in thorax)†
		Megacystis > 7 mm*
		Abdominal cysts
<i>Spine</i>		
Shape, closure		Scoliosis†
		Open spina bifida with myelomeningocele†
		Sacral agenesis†
		Sacro-occygeal teratoma†
<i>Limbs</i>		
Count of long-bone segments [Femur length]		Part of or whole limb missing†
Position of feet and hands		Clubfoot†, syndactyly†, polydactyly†
<i>Heart</i>		
Heart on same side of stomach	Equal size of chambers and heart-chamber filling (color/power Doppler)	Single ventricle*
	Crossing of outflow tracts (color/power Doppler)	Persisting bradycardia (heart block)
		Abnormal chambers, outflows†
<i>Other</i>		
		Excessive fluid: generalized hydrops/severe hydrothorax/severe pericardial effusion*
		Severe anomalies*:
		Severe skeletal dysplasia
		Syrenomelia
		Conjoined twins
		Amniotic band syndrome
		Body-stalk anomaly

*Severe anomaly considered 'not to be missed' at early scan. †Anomaly potentially detectable at early scan. BPD, biparietal diameter; HC, head circumference.

an information leaflet and an informed consent form. Participants were recruited between November 2012 and December 2015.

The scans were performed transabdominally, unless the transvaginal route was preferred or considered necessary. Prior to commencement of the study, all sonographers underwent training to improve their skills in late first-trimester fetal anatomy examination. The anatomical survey was performed following a structured protocol, aimed at excluding or diagnosing severe anomalies considered 'not to be missed' along with other severe, but less obvious, anomalies (Table 1).

In addition to women opting for CT, all women with an increased *a-priori* risk of congenital anomalies (e.g. positive family history, diabetes, use of teratogenic drugs), who are usually referred to a fetal medicine unit

for detailed ultrasound examination, were offered the early 12–13-week scan and enrolled in the study. All women with a continuing pregnancy were offered, as part of the 'usual care', a 20-week anomaly scan. All study data were extracted from local databases (Astraia or Mosos-U). Pregnancy outcomes and information on additional investigations (e.g. genetic investigations, delivery or pathology reports) were obtained from the hospital databases, returned follow-up forms provided to patients or the ultrasound practices, well-baby clinics and referring midwives or physicians.

All sonographers involved in the study kept a logbook documenting the start and end times of all early scans. For each early scan, an extra 15 min was scheduled, in addition to the 30 min allocated for the CT.

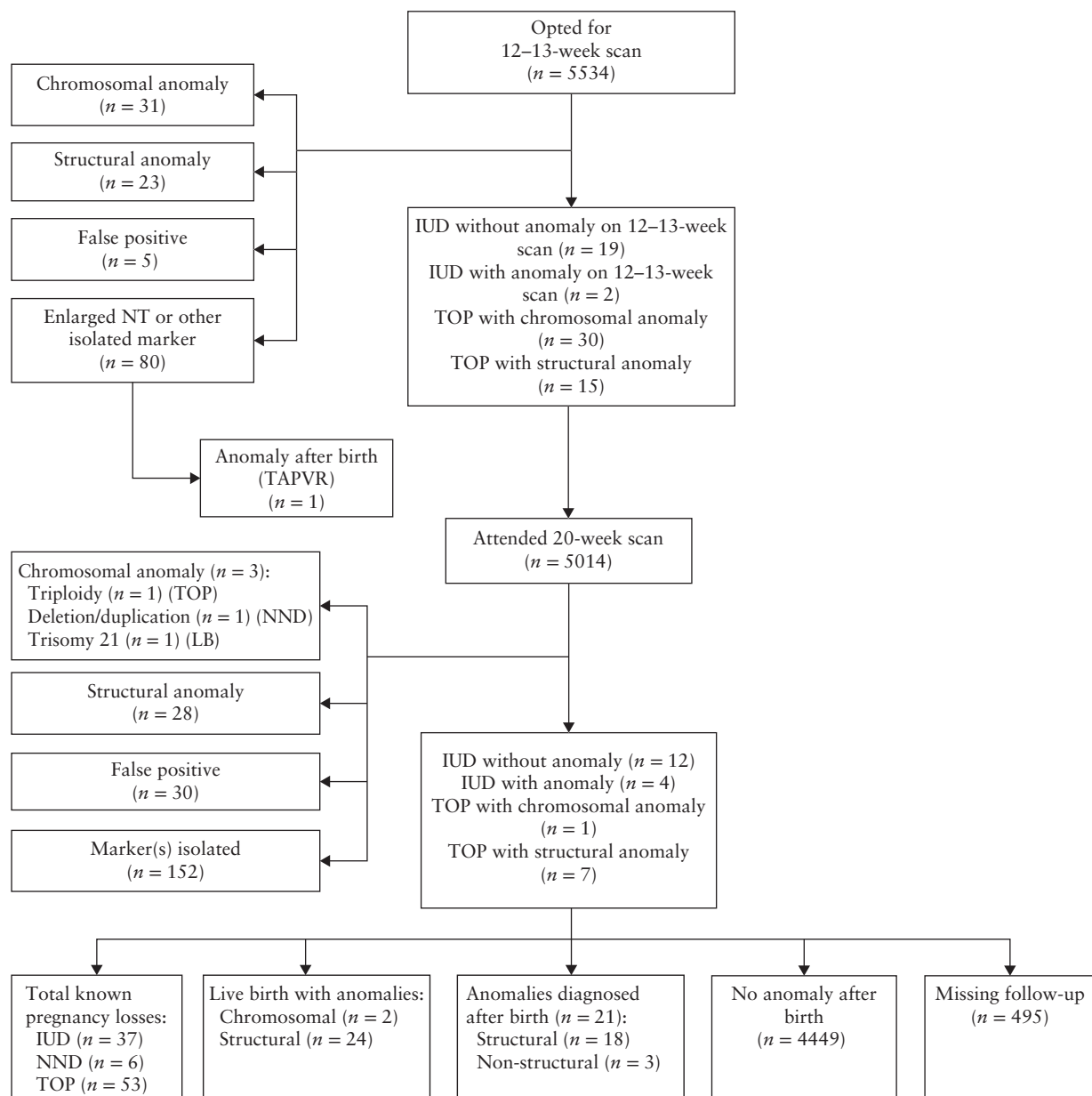


Figure 1 Flowchart showing findings and pregnancy outcome of 5534 pregnant women undergoing early scan at 12–13 weeks' gestation and 5014 attending 20-week anomaly scan. IUD, intrauterine death; NND, neonatal death; NT, nuchal translucency; TAPVR, total anomalous pulmonary venous return; TOP, termination of pregnancy.

Descriptive statistics on patients' characteristics and study findings, including frequencies, means, median and ranges were calculated in Excel (Microsoft Corp., Redmond, WA, USA).

RESULTS

A total of 5534 women underwent the early scan, including 5237 women who had opted for CT and 297 with an increased *a-priori* risk of fetal anomaly based on their history. The early scans were performed at a mean gestational age of 12 + 5 (range, 11 + 0 to 13 + 6) weeks. Mean maternal age was 32 (range, 17–53) years. An overview of the number of early scans, 20-week scans, findings and pregnancy outcomes is given in Figure 1. The average additional time required to perform the anatomical survey in women undergoing the CT was 12 (range, 9–18) min.

Structural anomalies

A total of 51 structural anomalies were diagnosed prenatally in chromosomally normal fetuses, 23 (45.1%) at the early scan and 28 (54.9%) at the 20-week scan. Details of the structural anomalies detected on the 12–13-week scan and the associated NT measurements are provided in Table S1. NT was increased in 12/23 (52.2%) of the cases diagnosed with a structural anomaly.

Details of structural anomalies detected prenatally, time of diagnosis and pregnancy outcome are shown in Table 2. Overall, 103 (18.6/1000 participants) anomalies were diagnosed during pre- or postnatal life, comprising 34 (32.4%) chromosomal and 69 (67.0%) structural anomalies. All 34 aneuploidies in the study population were diagnosed prenatally. With respect to structural anomalies, 51 (73.9%) were diagnosed before and 18 (26.1%) after birth (Tables 2, S2 and S3). Of the 12 cases of heart defect in the study population, four (33.3%) were detected at the 12–13-week scan, five (41.7%) at the 20-week scan and three (25.0%) after birth.

Although care was taken in tracing all severe anomalies observed after birth, under-reporting of minor anomalies by parents or of anomalies (such as minor cardiac ones) detected after the follow-up form had been returned, cannot be excluded.

Overall, the anomalies detected at the early scan were more severe than those detected at the 20-week scan. Of the anomalies 'not to be missed', all were detected at the early scan.

Chromosomal anomalies

A total of 34 chromosomal anomalies (6.1/1000 participants) were diagnosed in the study population, all diagnosed prenatally (Figure 1). In 33/34 (97.1%) of these, either the NT or the CT risk was increased

Table 2 Structural anomalies detected prenatally in euploid fetuses, at early scan (12–13 weeks; *n* = 5534 women), 20-week scan (*n* = 5014 women) and after birth, and pregnancy outcome

Anomaly	12–13-week scan (TOP)	20-week scan (TOP)	After birth	IUD	NND	LB
CNS (5)						
Acrania/anencephaly	3 (2)				1	
SB	1 (1)					
SB + acrania/anencephaly	1 (1)					
Heart (12)						
Complex	1 (1)	1 (1)				
TGA	1	1	1			3
ToF	1 (1)*	2 (1)				1
TAPVR			1			1
VSD	1	1	1			3
Abdominal wall (3)						
Omphalocele	1					1
Gastroschisis	2 (1)					1
Intestinal (3)		1	2			3
MCA (4)	4 (3)			1		
Skeletal (4)						
Severe	1 (1)	1 (1)				
Less severe	1	1				2
Hydrops (3)	1 (1)	2 (1)		1		
Kidneys/high urinary tract (7)	1 (1)	6 (2)				4
Bladder/low urinary tract (3)	3 (2)				1	
Clubfoot (8)		6	2			8
Schisis (5)		4	1†			5
Genetic syndrome (5)		2 (1)	3‡		1	3
Other (7)			7			7
Total	23 (15)	28 (7)	18	2	3	42

*22q11 deletion. †Only lip. ‡One case of Klippel–Trenaunay syndrome. CNS, central nervous system; IUD, intrauterine death; LB, live birth; MCA, multiple congenital anomalies; NND, neonatal death; SB, spina bifida; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; ToF, tetralogy of Fallot; TOP, termination of pregnancy; VSD, ventricular septal defect.

Table 3 Chromosomal anomalies diagnosed in study population, time of diagnosis and reason for testing (increased nuchal translucency (NT) measurement, increased risk on combined test (CT), carriership, suspicious findings on ultrasound)

Chromosomal anomaly	n	Reason for testing		
		NT > p95	High-risk CT	Anomalies at ultrasound
12–13-week scan (n = 31)				
47,XXX	1 (LB)	Y	N	NT > 3.5 mm
Trisomy 13	1	N	Y	Median cleft
Mosaic 45,X0/46,XY	1	Y	Y	Large NT, hydrops
Mosaic trisomy 16	1	Y	Y	Omphalocele, large NT, abnormal DV
Unbalanced translocation chr 4/15 (parent carrier)	1	Y	N	Increased NT very early
Triploidy	1	N	Y	Intracardiac focus, growth restriction
Triploidy	1	N	Y	Asymmetrical growth restriction
Trisomy 18	5	Y	Y	Hydrops, omphalocele, VSD, tachycardia, abnormal DV (n = 1); hydrops (n = 2); omphalocele (n = 1); omphalocele, abnormal four-chamber view (n = 1)
Trisomy 18	1	Not measured	Not calculated	Abnormal four-chamber view
Trisomy 21	16	Y	Y	Only increased NT (n = 4); increased NT + markers (n = 12)*
Trisomy 21	2	Y	Not calculated	Tricuspid regurgitation (n = 1); hydrothorax (n = 1)
After 20-week scan (n = 3)				
Deletion 2q37.3, duplication 11p15.5p15.2	1 (NND)	N	Not calculated	Macrosomia, hypertelorism, polyhydramnios
Triploidy	1	N	Y	Growth restriction, VSD, rocker-bottom feet†
Trisomy 21	1 (LB)	N	Y	Growth restriction, echogenic bowel‡
Total	34			
	LB (n = 2)	Increased (n = 27)	High risk (n = 28)	
	NND (n = 1)	Not increased (n = 6)	Normal NT (n = 2)	
	TOP (n = 31)	Not measured (n = 1)	Not calculated (n = 4)	

Outcome was termination of pregnancy (TOP) unless indicated otherwise. *Including two cases with additional structural anomaly (clubfoot (n = 1), atrioventricular septal defect (n = 1)). †Cell-free DNA analysis showed no increased risk. ‡Diagnosed at 29 weeks. chr, chromosome; DV, ductus venosus; LB, live birth; N, No; NND, neonatal death; p95, 95th percentile; VSD, ventricular septal defect; Y, yes.

(≥ 1:200), and in 31 of these 33 (91.2% of the total) the diagnosis was made in the first trimester. In the first case not diagnosed in the first trimester, the parents opted for cfDNA analysis instead of invasive testing; the anomaly (triploidy) was not identified by cfDNA analysis and was diagnosed later in pregnancy, owing to abnormal ultrasound findings prompting an amniocentesis. In the second such case, the couple had declined early invasive prenatal diagnosis, and trisomy 21 was diagnosed after an amniocentesis performed at 29 weeks' gestation, following the detection of structural anomalies. In the remaining only (1/34) case of true late diagnosis (deletion/duplication), NT was not increased and CT risk was not assessed and structural anomalies were seen only at the 20-week scan. Details of the chromosomal anomalies, observed associated structural anomalies and time of diagnosis are reported in Table 3.

False-positive diagnoses and isolated markers

Of the 5534 early scans and 5014 20-week scans performed, anomalies were detected but not confirmed at subsequent scans (false-positives) in five (0.1%) and

30 (0.6%) cases, respectively (Tables 4 and 5). Isolated ultrasound markers were observed at the early scan (excluding enlarged NT) and at the 20-week scan in 31 (0.6%) and in 152 (3.0%) cases, respectively (Table 6).

Pregnancy outcome

In 4661 fetuses, no anomalies were observed at the 20-week scan and the pregnancy outcome was uneventful. Spontaneous pregnancy loss occurred in 37 cases (0.7%); in 21 cases, intrauterine death (IUD) occurred before the 20-week scan and involved two fetuses with structural anomaly and 19 without anomaly detected on the early scan, while in 16 cases, IUD occurred after the 20-week scan and included four fetuses with anomaly and 12 without detected anomaly (Figure 1). In 53 cases the pregnancy was terminated. This occurred in 31/34 (91.2%) cases with chromosomal anomalies and in 22/51 (43.1%) pregnancies with structural anomalies. The majority of TOP for structural anomalies followed a first-trimester diagnosis (15/22, 68.2%) of the anomaly. Overall, parents opted for TOP in 15/23 (65.2%) cases of early-diagnosed structural anomaly, and in 7/28 (25.0%)

Table 4 False-positive structural anomaly findings on 12–13-week scan in 5534 pregnant women

Finding	Time of initial (false) diagnosis (weeks)	Time of final (normal) diagnosis (weeks)	n	Outcome
Echogenic choroid plexus	12 + 3	13 + 2	1	LB
Omphalocele	11 + 1*	15 + 2	1	LB
Discrepancy in size of great vessels	12 + 5	15 + 3	1	LB
Megacystis	12 + 2	14 + 2	1	LB
Intra-abdominal cyst	12 + 1	19 + 3	1	LFU
Total			5	

*Physiological gut herniation. LB, live birth with no anomaly; LFU, lost to follow-up.

Table 5 False-positive structural anomaly findings on 20-week scan in 5014 pregnant women

Finding	n	Outcome
Anal/bowel	1	LB
Uncertain cardiac findings	8	LB
Asymmetric brain ventricles	1	LB
Miscellaneous*	16	LB
Urogenital	1	LB
Spine	1	LB
Echogenic lungs	2	LB
Total	30	

*Abnormal biometry, abnormal amniotic fluid. LB, live birth with no anomaly.

Table 6 Markers for structural anomalies observed at 12–13-week scan ($n = 5534$ women) and at 20-week scan ($n = 5014$ women)

Marker	n	Outcome
<i>12–13-week scan</i>		
Single umbilical artery	19	15 LB, 4 LFU
Absent nasal bone	1	1 LB
Pyelectasis	3	3 LB
Echogenic bowel	2	2 LB
Other first-trimester markers*	6	6 LB
Total	31	
<i>20-week scan</i>		
Single umbilical artery	21	1 IUD, 20 LB
Ventriculomegaly	8	8 LB
Pyelectasis	27	27 LB†
Echogenic bowel	12	12 LB
Choroid plexus cyst	6	6 LB
Echogenic heart focus	17	17 LB‡
Multiple markers	4	1 TOP, 3 LB
Short femur	5	5 LB
Marker not specified	52	11 LB, 41 LFU
Total	152	

*Abnormal ductus venosus flow, tricuspid regurgitation.

†Pyelectasis ($n = 2$), congenital heart defect ($n = 1$). ‡Hand anomaly ($n = 1$). LB, liveborn with no anomaly; LFU, lost to follow-up after birth; TOP, termination of pregnancy.

of those diagnosed at the 20-week scan. Neonatal death occurred in six cases.

DISCUSSION

This study shows that an early scan impacts on the time of detection of congenital anomalies and on parental

decisions. In fact, 45% of the prenatally diagnosed anomalies, including all the lethal ones, in the population could be diagnosed in the first trimester. Parents opted for TOP in 83.3% of the early-diagnosed anomalies, as opposed to in 25.8% of those diagnosed late. The incidence of false-positive results leading to unnecessary parental anxiety was 0.1% at the early scan, six times lower than that at the 20-week scan.

The prevalence of anomalies detected early (1.0%) is similar to that found in another large study, suggesting no diagnostic bias⁶. Interestingly, of the 34 chromosomal anomalies, only one (deletion/duplication without obvious anomalies) was not diagnosed by either an enlarged NT and/or increased risk on CT.

The detection rate achieved confirms that early scans performed by trained sonographers can detect around 40–50% of structural anomalies in an unselected population⁵. In line with previous reports, we have shown that, in particular, severe anomalies are amenable to early diagnosis, as can be inferred by the high number of TOPs, fetal and neonatal losses and low number of live births in the early-diagnosis group^{5,13–15}.

Early TOP was carried out on average at 15 weeks' gestation, after additional investigations and repeat scans had been performed. There is evidence that early TOP is less traumatic for the mother than when carried out at a stage at which fetal movements are already felt, or at a time when legal limits for TOP (usually 20–24 weeks) may push parents into making a rushed decision¹⁶. Moreover, the number of false positives and markers is much lower at the early scan, limiting parental anxiety^{11,17}. Hence, the study confirms the value of an increased NT, observed in over 50% of the early-diagnosed anomalies, as a marker of abnormal development^{18,19}.

cfDNA analysis is offered increasingly as a second- or first-tier screening test⁵. The question arises as to whether an early 'anomaly' scan should also be part of an up-to-date screening policy²⁰. All pregnant women undergo dating scans; however, in order to maximize detection of anomalies, these should be carried out after 12 weeks' gestation, when ossification of the skull is complete¹⁸ and physiologic bowel herniation is resolved¹⁹. The scan should be performed by sonographers experienced in first-trimester ultrasound and adhering to a structured protocol^{9,21}.

Policy makers may argue on the cost-effectiveness of this additional scan^{10,22}. Besides psychological aspects and

patient preference^{17,23}, an early (transvaginal) scan may be preferred, especially for heart examination, to a highly unsatisfactory 20-week scan, in women with high body mass index and at higher risk of congenital anomalies^{24,25}.

However, there are arguments that cfDNA screening (and the associated scan) should be postponed for 1–2 weeks, from 10 to 12 weeks' gestation. First, younger women – the majority of those at reproductive age – have a higher chance of structural rather than chromosomal anomalies; second, this may save unnecessary costs in case of fetal demise; third, it may reduce the number of test failures due to low fetal fraction; fourth, the coincidental finding of a large NT would call for a more advanced genetic examination^{26,27}; and fifth, it may prevent false-negative cfDNA results in cases of trisomy 18, trisomy 13, Turner syndrome and triploidy^{9,28,29}.

If the early scan becomes standard practice, the remaining question is whether the 20-week scan should be revisited to include a detailed re-examination of only organs, such as brain and heart, that are still developing or can be better visualized later in pregnancy.

In conclusion, policy-makers faced with the challenge of devising an up-to-date screening strategy aimed at maximizing anomaly detection and reproductive choices of parents, should balance the costs of an additional early scan with the advantages of early diagnosis of fetal anomalies.

REFERENCES

- Gezondheidsraad. *Wet bevolkingsonderzoek: prenatale screening op downsyndroom en neuralebuisdefecten*. Publicatienr. 2007/05WBO. Gezondheidsraad: Den Haag, Netherlands, 2007.
- Health Council of the Netherlands. *Prenatal Screening (2): Down's syndrome, neural tube defects*. Publication no. 2004/06. Health Council of the Netherlands: The Hague, the Netherlands, 2004.
- Bakker M, Birnie E, Pajkrt E, Bilardo CM, Snijders RJ. Low uptake of the combined test in The Netherlands – which factors contribute? *Prenat Diagn* 2012; 32: 1305–1312.
- Crombag NM, Boeije H, Iedema-Kuiper R, Schielen PC, Visser GH, Bensing JM. Reasons for accepting or declining Down syndrome screening in Dutch prospective mothers within the context of national policy and healthcare system characteristics: a qualitative study. *BMC Pregnancy Childbirth* 2016; 16: 121.
- Health Council of the Netherlands. *Population Screening Act: Non-Invasive Prenatal Test (NIPT) as initial test for Down's, Patau's and Edwards' syndrome*. Publication no. 2016/10. Health Council of the Netherlands: The Hague, the Netherlands, 2016.
- Syngelaki A, Chelmen T, Dagklis T, Allan L, Nicolaidis KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. *Prenat Diagn* 2011; 31: 90–102.
- Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, Lau TK, Papageorgiou AT, Raine-Fenning NJ, Stirnemann J, Suresh S, Tabor A, Timor-Tritsch IE, Toi A, Yeo G. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2013; 41: 102–113.
- Nicolaidis KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. *Prenat Diagn* 2011; 31: 3–6.
- Karim JN, Roberts NW, Salomon LJ, Papageorgiou AT. Systematic review of first-trimester ultrasound screening for detection of fetal structural anomalies and factors that affect screening performance. *Ultrasound Obstet Gynecol* 2017; 50: 429–441.
- Harper LM, Wood SL, Jenkins SM, Owen J, Biggio JR. The Performance of First-Trimester Anatomy Scan: A Decision Analysis. *Am J Perinatol* 2016; 33: 957–965.
- Storm JR. [Main points in the Population Screening Law]. *Ned Tijdschr Geneesk* 1996; 140: 1776–1778. [Article in Dutch].
- Colosi E, Musone R, Filardi G, Fabbo A. First trimester fetal anatomy study and identification of major anomalies using 10 standardized scans. *J Prenat Med* 2015; 9: 24–28.
- Grande M, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers. *Ultrasound Obstet Gynecol* 2012; 39: 157–163.
- Saltvedt S, Almström H, Kublickas M, Valentin L, Grunewald C. Detection of malformations in chromosomally normal fetuses by routine ultrasound at 12 or 18 weeks of gestation – a randomised controlled trial in 39,572 pregnancies. *BJOG* 2006; 113: 664–674.
- Rossi AC, Prefumo F. Accuracy of ultrasonography at 11–14 weeks of gestation for detection of fetal structural anomalies: a systematic review. *Obstet Gynecol* 2013; 122: 1160–1167.
- Korenromp MJ, Christiaens GC, van den Bout J, Mulder EJ, Hunfeld JA, Bilardo CM, Offermans JP, Visser GH. Long-term psychological consequences of pregnancy termination for fetal abnormality: a cross-sectional study. *Prenat Diagn* 2005; 25: 253–260.
- Filly RA. Obstetrical sonography: the best way to terrify a pregnant woman. *J Ultrasound Med* 2000; 19: 1–5.
- Fleurke-Rozema JH, van Leijden L, van de Kamp K, Pajkrt E, Bilardo CM, Snijders RJ. Timing of detection of anencephaly in The Netherlands. *Prenat Diagn* 2015; 35: 483–485.
- Timor-Tritsch IE, Warren WB, Peisner DB, Pirrone E. First-trimester midgut herniation: a high-frequency transvaginal sonographic study. *Am J Obstet Gynecol* 1989; 161: 831–833.
- Alfirevic Z, Bilardo CM, Salomon LJ, Tabor A. Women who choose cell-free DNA testing should not be denied first-trimester anatomy scan. *BJOG* 2017; 124: 1159–1161.
- Iliescu D, Tudorache S, Comanescu A, Antsaklis P, Cotarcea S, Novac L, Cernea N, Antsaklis A. Improved detection rate of structural abnormalities in the first trimester using an extended examination protocol. *Ultrasound Obstet Gynecol* 2013; 42: 300–309.
- Pilalis A, Basagiannis C, Eleftheriades M, Faros E, Troukis E, Armelidou E, Papastefanou I, Souka AP. Evaluation of a two-step ultrasound examination protocol for the detection of major fetal structural defects. *J Matern Fetal Neonatal Med* 2012; 25: 1814–1817.
- Maiz N, Burgos J, Barbazán MJ, Recio V, Martínez-Astorquiza T. Maternal attitude towards first trimester screening for fetal abnormalities. *Prenat Diagn* 2016; 36: 449–455.
- Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009; 301: 636–650.
- Paladini D. Sonography in obese and overweight pregnant women: clinical, medicolegal and technical issues. *Ultrasound Obstet Gynecol* 2009; 33: 720–729.
- Grande M, Jansen FA, Blumenfeld YJ, Fisher A, Odibo AO, Haak MC, Borrell A. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; 46: 650–658.
- Evans MI, Wapner RJ, Berkowitz RL. Noninvasive prenatal screening or advanced diagnostic testing: caveat emptor. *Am J Obstet Gynecol* 2016; 215: 298–305.
- Wagner P, Sonek J, Hoopmann M, Abele H, Kagan KO. First-trimester screening for trisomies 18 and 13, triploidy and Turner syndrome by detailed early anomaly scan. *Ultrasound Obstet Gynecol* 2016; 48: 446–451.
- Kagan KO, Schmid M, Hoopmann M, Wagner P, Abele H. Screening Performance and Costs of Different Strategies in Prenatal Screening for Trisomy 21. *Geburtshilfe Frauenheilkd* 2015; 75: 244–250.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Structural anomalies diagnosed at the early scan performed at 12–13 weeks' gestation in 5534 women, and their relationship with nuchal translucency

Table S2 Proportion of structural anomalies detected on early (12–13 weeks' gestation) scan, 20-week scan and after birth

Table S3 Structural anomalies detected after birth



This article has been selected for Journal Club.

A slide presentation, prepared by Dr Fiona Brownfoot, one of UOG's Editors for Trainees, is available online.

Chinese translation by Dr Yang Fang.
Spanish translation by Dr Rubén Darío Fernández.



Eficacia de la ecografía de 12–13 semanas para el diagnóstico temprano de anomalías congénitas fetales en la era del ADN fetal

RESUMEN

Objetivos El objetivo principal de este estudio fue evaluar la proporción y el tipo de anomalías congénitas, tanto estructurales como cromosómicas, que se pueden detectar en una ecografía temprana realizada a las 12–13 semanas de gestación, en comparación con la ecografía a las 20 semanas para detectar anomalías estructurales que se ofrece bajo la política de cribado actual. Los objetivos secundarios fueron evaluar la incidencia de falsos positivos y de marcadores ecográficos en ambas ecografías, y la elección de los padres con respecto a la interrupción legal del embarazo (ILE).

Métodos Se invitó a especialistas en técnicas de ecografía acreditados(as) para la medición de la translucencia nuchal (TN) a que participasen en el estudio, después de recibir formación adicional para mejorar su experiencia en el examen de la anatomía fetal de finales del primer trimestre. Las ecografías tempranas se realizaron bajo un protocolo estructurado en seis clínicas de ultrasonido y dos centros de especialistas en el noreste de los Países Bajos. A todas las mujeres que optaron por la prueba combinada (PC) o con un mayor riesgo a priori de anomalías fetales, se les ofreció una ecografía a las 12–13 semanas de gestación (grupo de estudio). A todas las mujeres que continuaron con la gestación, se les ofreció, como parte del ‘cuidado habitual’, una ecografía a las 20 semanas para detectar posibles anomalías.

Resultados El grupo de estudio consistió en 5237 mujeres que optaron por la PC y 297 mujeres con un mayor riesgo a priori de anomalías (5534 en total). En total, se detectaron 51 anomalías prenatales estructurales y 34 cromosómicas en la población de estudio y 18 anomalías estructurales adicionales después del nacimiento. En total, se detectaron 54/85 (63.5%) anomalías en la ecografía temprana (23/51 (45.1%) anomalías estructurales y todas las cromosómicas que presentaban o un mayor riesgo en el cribado del primer trimestre o anomalías estructurales (31/34)). En la ecografía temprana se detectaron todas las anomalías particularmente graves (todos los casos con defectos del tubo neural, onfalocelo, megavejiga y anomalías múltiples graves congénitas o del esqueleto). La TN se incrementó en 12/23 (52.2%) casos de anomalía estructural detectada en la ecografía temprana. De los 12 casos de defectos cardíacos, cuatro (33.3%) se detectaron en la ecografía temprana, cinco (41.7%) en la ecografías de 20 semanas y tres (25.0%) después del nacimiento. Los falsos positivos en la ecografía temprana y en la ecografía de 20 semanas ocurrieron en el 0,1% y el 0,6% de los casos, respectivamente, mientras que los marcadores ecográficos se detectaron en el 1,4% y 3,0% de los casos, respectivamente. Después del diagnóstico de una anomalía en el primer o segundo trimestre, los padres eligieron la ILE en el 83,3% y 25,8% de los casos, respectivamente.

Conclusiones Una ecografía temprana realizada entre las 12–13 semanas de gestación por especialistas competentes en ecografía puede detectar aproximadamente la mitad de las anomalías estructurales prenatales detectables y el 100% de las que se espera que se detecten en esta etapa. Las anomalías particularmente graves, que a menudo provocan que los padres elijan la ILE, son susceptibles de un diagnóstico temprano. La ecografía temprana es una parte esencial de la atención moderna del embarazo.

在游离 DNA 时代通过孕 12~13 周扫描早期诊断胎儿先天畸形的有效性

目的: 本研究的主要目的是评估孕 12~13 周早期扫描能够发现的先天异常（结构和染色体）的比例和类型，并与目前筛查政策下 20 周结构异常扫描进行比较。次要目的是评估假阳性结果发生率和 2 次扫描的超声标志物，以及父母对终止妊娠（termination of pregnancy, TOP）的选择。

方法: 参与本研究的超声医师均具备颈项透明层（nuchal translucency, NT）测量技能认证，在接受额外培训提高孕早期末胎儿解剖检查技能后，在荷兰东北部的 6 个超声检查部门和 2 个转诊中心，根据结构化方案进行早期扫描。所有选择进行联合检测（combined test, CT）或胎儿畸形先验风险增加的孕妇在孕 12~13 周进行扫描（研究组）。所有继续妊娠的孕妇接受孕 20 周畸形扫描（“常规检查”的一部分）。

结果: 研究组包括选择 CT 检查的 5237 例孕妇和畸形先验风险升高的 297 例孕妇（共 5534 例）。研究人群中产前检查共发现 51 例结构异常和 34 例染色体异常，出生后又另外发现 18 例结构异常。共 63.5%（54/85）的异常在早期扫描时发现，45.1%（23/51）的结构异常和所有的染色体异常表现为孕早期筛查风险增加或结构异常（31/34）。早期扫描发现所有特别严重的畸形（所有神经管缺陷、脐膨出、巨膀胱、多发严重先天性和严重骨骼畸形病例）。52.2%（12/23）的早期扫描发现的结构异常病例中 NT 增厚。12 例心脏缺陷病例中，4 例（33.3%）在早期扫描时发现，5 例（41.7%）在孕 20 周扫描时发现，3 例（25.0%）在出生后发现。早期扫描和孕 20 周扫描时诊断假阳性率分别为 0.1% 和 0.6%，然而分别在 1.4% 和 3.0% 的病例中发现超声标志物。在孕早期和孕中期诊断畸形后，分别有 83.3% 和 25.8% 的病例父母选择终止妊娠。

结论: 由经验丰富的超声医生在孕 12~13 周进行早期扫描，能够发现近一半的产前可检测的结构异常，人们希望在这一阶段发现所有畸形。应该早期诊断特别严重的畸形，父母常因此选择终止妊娠。早期扫描是现代产科保健必不可少的一部分。