National implementation of the first-trimester anomaly scan: benefits, opportunities and challenges

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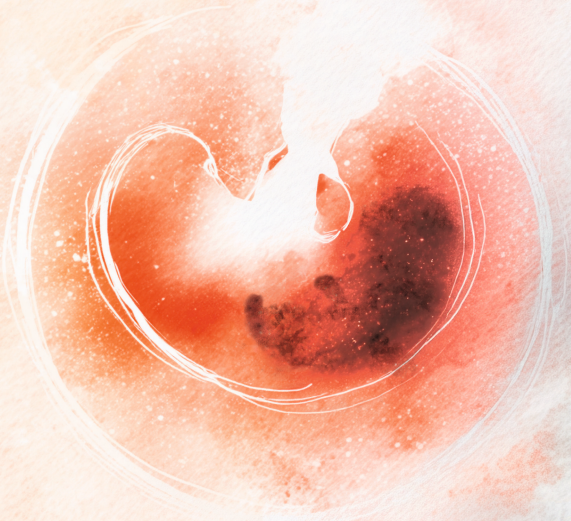

CHAPTER 3

Introduction of a nationwide first-trimester anomaly scan in the Dutch national screening program

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ABSTRACT

Background

A significant proportion of major fetal structural anomalies can be detected in the first trimester by ultrasound examination. However, the test performance of the first-trimester anomaly scan (FTAS) performed in a low-risk population as part of a nationwide prenatal screening program is unknown. Potential benefits of the FTAS include early detection of fetal anomalies, providing parents with more time for reproductive decision-making.

Objectives

To investigate the uptake, test performance and time to a final prenatal diagnosis after referral.

Study design

A nationwide implementation study was conducted in the Netherlands (November 2021-November 2022). The FTAS was performed between 12+3 and 14+3 weeks gestation by certified sonographers using a standard protocol. Women were referred to a tertiary care center if anomalies were suspected. Uptake, test performance and time to a final prenatal diagnosis (days between referral and date of final diagnosis/ prognosis for reproductive decision-making) were determined. Test performance was calculated for first-trimester major congenital anomalies, such as anencephaly and holoprosencephaly and all diagnosed anomalies <24 weeks gestation.

Results

The FTAS uptake was 74.9% (129 704/173 129). In 1.0% (1 313/129 704), an anomaly was suspected, of which 54.9% (n=721) had abnormal findings on the detailed first-trimester diagnostic scan and 44.6% (n=586) showed normal results. In 0.5% (n=6), intra-uterine fetal death occurred. In the total group of 721 cases with abnormal findings, 332 structural anomalies, 117 genetic anomalies, 82 other findings (abnormal fetal biometry, sonomarkers, placental/umbilical cord anomaly, an-/oligohydramnios) and 189 cases with transient findings (defined as ultrasound findings which resolved <24 weeks gestation) were found, with one case having an unknown outcome. 0.9% (*n*=1164) of all cases with a normal FTAS were diagnosed with a fetal anomaly in the second trimester. Test performance included a sensitivity of 84.6% (126/149) for first-trimester major congenital anomalies and 31.6% (537/1701) for all types of anomalies. Specificity for all anomalies was 99.2% (98 055/98 830); positive predictive value 40.9% (537/1 312); negative predictive value 98.8% (98 055/99 219); positive likelihood ratio 40.3; negative likelihood ratio 0.7; false positive rate 0.8% (775/98 830) and false negative rate 68.4%

(1 164/1 701). The median time to diagnosis for structural anomalies was 20 days (6-43 days; median GA 16+3), for genetic anomalies 17 days (8.5-27.5 days; median GA 15+6 weeks) and for first-trimester major congenital anomalies 9 days (5-22 days; median GA 14+6 weeks).

Conclusions

The performance of a newly introduced nationwide FTAS in a low-risk population showed a high sensitivity for first-trimester major congenital anomalies and a lower sensitivity for all anomalies combined. The program was accompanied by a referral rate of 1.0%, of which 59.1% involved cases where anomalies were either not confirmed or resolved before 24 weeks gestation. Timing of diagnosis was around 16 weeks gestation for referred cases. To evaluate the balance between benefits and potential harm of the FTAS within a nationwide prenatal screening program, it is essential to assess the effectiveness of the program over time and to consider the perspectives of both women and their partners, as well as healthcare professionals.

INTRODUCTION

A congenital structural anomaly is diagnosed in 2.5% of pregnancies.[1] In most developed countries, a second-trimester anomaly scan (SAS) is offered as part of routine care.[2] There is increasing evidence that a significant proportion of major congenital anomalies can be detected in the first trimester by ultrasound.[3,4] A potential benefit of early detection is that it offers parents more time to make reproductive decisions. Several cohort studies evaluated the test performance of first-trimester fetal anomaly screening, mainly as part of the combined test. These studies described a sensitivity of 46.1%-47.8% and high specificity of 99.96% for the detection of major congenital anomalies in low-risk populations.[4,5] Yet, these studies included ultrasounds from secondary or tertiary care settings, performed by experienced sonographers,[4,5] which makes it difficult to compare with a national prenatal screening setting. Furthermore, reported detection rates vary considerably, which is explained by numerous factors, such as the absence of a standardized protocol or differences in gestational age (GA) at time of the scan.[4,6]

In the Netherlands, a nationwide prenatal screening program is offered to all pregnant women consisting of non-invasive prenatal testing (NIPT) as a first-tier test for aneuploidy, and the SAS, performed at GA 18-21 weeks.[7] Additionally, the Dutch guidelines on routine obstetric care advise to perform a dating scan at GA 10-12+6 weeks.[8] The first-trimester anomaly scan (FTAS) was introduced as a research protocol in September 2021 into the prenatal screening program to detect major congenital anomalies by means of the 'Implementation of first Trimester Anomaly Scan study'.[9]

Although the performance of the FTAS in the early detection of fetal anomalies is promising, its performance in a low-risk population in a nationwide prenatal screening program remains unknown. More importantly, before implementing the FTAS in a prenatal screening program, we need to explore whether the benefits of detecting fetal anomalies in an early stage outbalance undesired effects, such as anxiety caused by unjustified referrals or unclear ultrasound findings. We here present the first-year results of FTAS implementation as a nationwide screening test in the Netherlands.

MATERIALS AND METHODS

Study design

The Implementation of first Trimester Anomaly Scan (IMITAS) study is a prospective observational nationwide cohort study in the Netherlands evaluating introduction of the FTAS. Approval for the study was granted by the Dutch Ministry of Health, Welfare,

and Sport (license 3219987-1012059-PG) and by the Health Council of the Netherlands (2021/30).

Setting

Prenatal screening in the Netherlands is organized by the Center for Population Screening of the Dutch Institute for Public Health and Environment. All pregnant women, who expressed interest in prenatal screening were informed about the different tests and the additional possibility of the FTAS within the IMITAS study, by a certified obstetric healthcare professional. All prenatal tests including the FTAS were reimbursed by the government, except for NIPT (175 euros). Written informed consent was obtained prior to the FTAS and entered the national prenatal registration database (Peridos). The FTAS was performed by certified sonographers between GA 12+3-14+3 weeks (transabdominal and/or transvaginal) and a standardized screening protocol was used (Table 1). This period was chosen for optimal visualization of fetal anatomical structures and optimal positioning of the uterus for imaging. All prenatal counsellors and sonographers were trained before the start of the FTAS. Training of sonographers consisted of a theoretical and practical course with a mandatory exam. Moreover, active participation in audits, monitoring and other quality assessments were required.[10]

Participation and Inclusion

The FTAS was offered from September 1st 2021. We included the data of all women who underwent the FTAS between November 1st 2021 and November 1st 2022, considering the first two months as starting phase. A dating scan prior to the FTAS was required. Women who received an abnormal NIPT before the FTAS and women with a high risk for fetal anomalies were excluded, as they were directly offered a detailed diagnostic scan in a tertiary care center.

Follow-up

Women were referred to a tertiary care center for a detailed diagnostic scan if the FTAS resulted in: suspicion of a fetal structural anomaly; fetal biometry percentile <2.3 for any of the measured parameters; nuchal translucency ≥3.5mm; absent fetal bladder filling or longitudinal bladder diameter ≥7mm. Three outcome measures were possible: normal, incomplete, abnormal with referral to a tertiary care center. 'Incomplete' was entered if the sonographer was unable to visualize all mandatory ultrasound images, but the sonographer had no indication of a fetal anomaly. If the result was 'incomplete', the FTAS was not repeated, but followed by the SAS. This was chosen to avoid many unnecessary referrals in the first year of implementation. Results of the detailed diagnostic scans, diagnostic genetic testing and obstetric outcomes were collected at the tertiary care centers.

Table 1. First-trimester anomaly scan standardized screening protocol[21,22]

General characteristics
Number of fetuses Viability Amount of amniotic fluid Placental localization
Fetal growth parameters
Crown-rump-length (CRL, *measuring op to 84 mm*) Head circumference (HC) Abdominal circumference (AC) Femur length (FL)
Fetal anatomy
· **Skull** *Intactness and shape* · **Brain** *Visualization of midline and choroid plexus* · **Neck** *Nuchal translucency (NT) measurement* · **Spine** *Visualization of spine in sagittal plane* *Continuity of the skin* · **Face** *Profile* · **Thorax** *Shape of the thorax* *Aspect of the lungs* · **Heart** *Position of the heart* *Four-chamber view* · **Abdomen** *Abdominal wall and umbilical cord insertion* *Stomach and bladder filling* *Longitudinal bladder diameter (LBD)* · **Extremities** *Both upper- and lower extremities* *Presence of both hands* *Presence of both feet*

Outcomes

Outcome variables were uptake, test performance and time to a final prenatal diagnosis (in days) after referral because of a suspected anomaly at the FTAS. Although a standardized protocol was followed, if abnormal findings were suspected or if sonographers were in doubt, referral to a tertiary care center was allowed. Therefore, we calculated FTAS test performance for all anomalies diagnosed GA <24 weeks and for first-trimester major congenital anomalies. The moment of final diagnosis of a fetal anomaly was defined as the

date GA <24+0 weeks (the upper limit for termination of pregnancy in the Netherlands), at which sufficient knowledge on the prenatal diagnosis and prognosis was available to parents for reproductive decision-making. This was based on information from ultrasound reports and electronic patient files (Table A.1). Definitions of uptake and test performance are provided in Table 2. All anomalies diagnosed GA <24 weeks were categorized into structural anomalies; genetic anomalies; other findings (abnormal fetal biometry, sonomarkers, placental/umbilical cord anomaly, an-/oligohydramnios) and transient ultrasound findings. There was no overlap between cases. Cases with more than one anomaly in the same organ system were classified according to the most severe anomaly, but as a single organ system anomaly. Multiple congenital anomalies were defined as more than one structural anomaly in different organ systems.

Table 2. Definitions of uptake and test performance

Term	Definition	Calculation
Uptake	Percentage of pregnancies that had FTAS	Number of pregnancies that had an FTAS during the study period divided by total number of pregnancies as registered in the national database
True-positive	Anomaly is correctly identified by FTAS	Number of pregnancies with an abnormal FTAS and a confirmed suspected anomaly GA <24 weeks (including cases with intrauterine fetal demise at first detailed diagnostic scan)
False-positive	FTAS incorrectly suggests the presence of an anomaly	Number of pregnancies with an abnormal FTAS, but with a normal first detailed diagnostic scan + the number of pregnancies in which the ultrasound finding resolved GA <24 weeks
False-negative	FTAS incorrectly suggests the absence of an anomaly	Number of pregnancies in which an FTAS was performed without suspicion of an anomaly, but an anomaly was detected at SAS
True-negative	The absence of anomaly is correctly identified by FTAS	Number of pregnancies with a normal FTAS and normal SAS as registered in the national database
Sensitivity	Proportion of actual positives correctly identified by FTAS	True positives / true positives + false negatives
Specificity	Proportion of actual negatives correctly identified by FTAS	True negatives / true negatives + false positives
Positive predictive value	Proportion of positive test results that are true positives	True positives / true positives + false positives
Negative predictive value	Proportion of negative test results that are true negatives	True negatives / true negatives + false negatives

Table 2. (Continued)

Term	Definition	Calculation
Positive likelihood ratio	How much the odds of having the disease increase when FTAS is positive	Sensitivity / 1- specificity
Negative likelihood ratio	How much the odds of having the disease decrease when FTAS is negative	1-Sensitivity / specificity
False positive rate	Proportion of actual negatives that are incorrectly identified as positive by FTAS	False positives / false positives + true negatives
False negative rate	Proportion of actual positives that are incorrectly identified as negative by FTAS	False negatives / false negatives + true positives

Abbreviations: FTAS, First-trimester anomaly scan; GA, gestational age; SAS, second-trimester anomaly scan.

First-trimester major congenital anomalies

First-trimester major congenital anomalies were classified as severe structural anomalies that can be expected to be "always" diagnosed by FTAS (Figure 1). This classification was defined by the fetal medicine specialists of the IMITAS team (MB, MH, CB, ES, AC, AE, AG, GM, EP, SG, EL) and based on Syngelaki et al.[3]

First-trimester major congenital anomalies
Anencephaly
Encephalocele
Holoprosencephaly
Limb body wall complex
Omphalocele
Gastroschisis
Megacystis
Bladder exstrophy
Limb deformities
Twin Reversed Arterial Perfusion (TRAP)
Hydrops

Figure 1. First-trimester major congenital anomalies considered to be "always" detected by FTAS

Description: Classification defined by the fetal medicine specialists of the IMITAS team and based on Syngelaki et al.[3]
Abbreviations: FTAS, First-trimester anomaly scan.

Statistical Analysis

Descriptive statistics summarized baseline characteristics and primary outcomes. Normally distributed variables were described as mean ± standard deviation; non-normally distributed variables as median and interquartile range. Test performance was calculated using 2x2 tables. Subgroups were compared in IBM SPSS statistics version 29 using Independent Samples T-Test for normally distributed numerical variables, Mann-

Whitney U test for non-normally distributed numerical variables and Chi-squared test for categorical variables. Significance was determined at P<0.05.

RESULTS

Uptake and referral after FTAS

During the study period, the FTAS was performed in 129 704/173 129 pregnancies resulting in an uptake of 74.9%. Baseline characteristics are presented in Table 3. No relevant differences in baseline characteristics were found between women with a normal and abnormal FTAS result (Table A.2).

In total, 1 313 (1.0%) pregnancies were referred to a tertiary care center for a detailed diagnostic scan (Figure 2, Table 4).

Table 3. Baseline characteristics (*n*=129 704)

Characteristics	Values
Maternal age, years (mean ± SD)[a]	30.8±4.5
BMI (median, IQR)[b]	24.1 (6.1)
Parity, *n* (%)[c]	
0	59 290 (47.3)
≥1	66 035 (52.7)
Singleton pregnancy, *n* (%)	128 109 (98.8)
GA at FTAS (weeks), *n* (%)[d]	
12+1 – 12+2	219 (0.2)
12+3 – 13+0	25 600 (20.3)
13+1 – 13+5	60 933 (48.4)
13+6 – 14+3	37 669 (29.9)
14+4 – 14+5	1 438 (1.1)
NIPT performed, *n* (%)	89 325 (68.9)

Abbreviations: BMI, Body Mass Index; IQR, Interquartile Range; GA, Gestational Age; FTAS, First-trimester anomaly scan; NIPT, Non-Invasive Prenatal Testing.
[a]Maternal age: missing 64
[b]BMI: missing 7 472
[c]Parity: missing 4 379
[d]GA at FTAS: missing 3 845. In accordance with national agreements, it was possible to offer the FTAS in exceptional cases up to two days before or after the specified period to pregnant women who were unable to undergo the FTAS within the specified period.

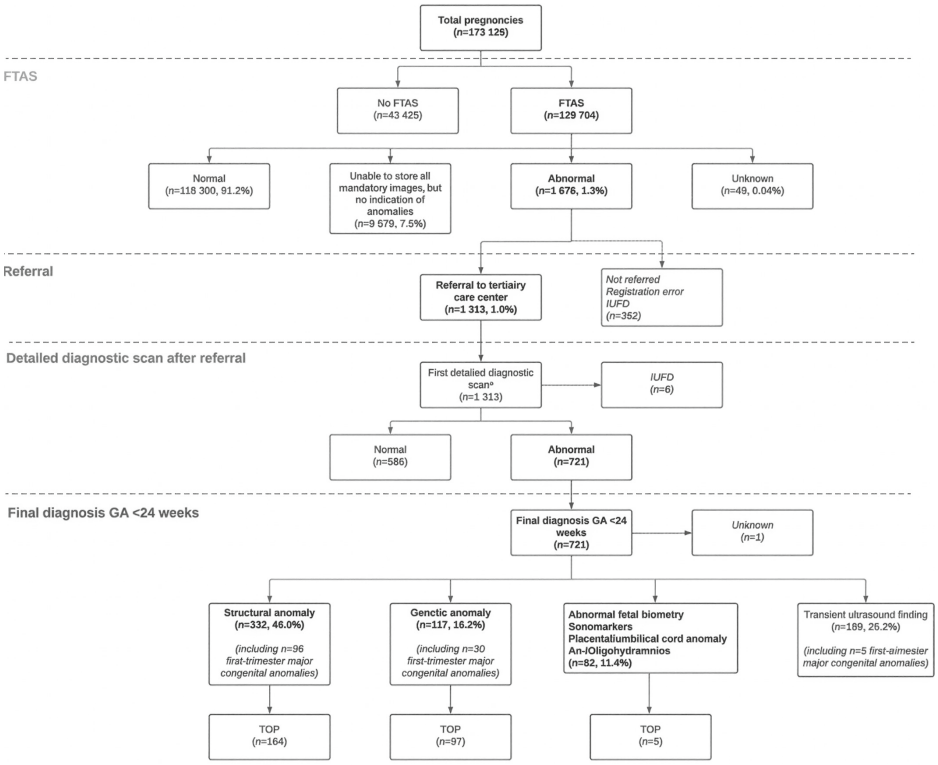

Figure 2. Flowchart of all pregnancies that had the FTAS in the IMITAS study

Description: [a]Performed in tertiary care center.

Abbreviations: FTAS, First-trimester anomaly scan; IMITAS, Implementation of first Trimester Anomaly Scan; IUFD, Intrauterine fetal demise; GA, gestational age; TOP, termination of pregnancy.

Tabel 4. Reason for referral after abnormal FTAS (*n*=1 313)

Reason for referral	Total *n* (%)
Structural anomaly	***673 (51.3)***
Heart	143 (21.2)
Central nervous system	107 (15.9)
Abdomen	91 (13.5)
Urogenital system	71 (10.5)
MCA	65 (9.7)
Extremities	64 (9.5)
Face	51 (7.6)
Hydrops/ascites	26 (3.9)
Skeletal	21 (3.1)
Thorax/lungs	18 (2.7)
Neck	16 (2.4)
Abnormal fetal biometry	***374 (28.5)***
Sonomarker	***230 (17.5)***
Increased NT (≥3.5mm)	178 (77.4)
Hypoplasia/aplasia nasal bone	14 (6.1)
Echogenic bowel	11 (4.8)
Choroid plexus cyst	10 (4.3)
Single umbilical artery	7 (3.0)
≥2 sonomarkers	7 (3.0)
Cardiac echogenic focus	3 (1.3)
Placental/umbilical cord/amniotic fluid anomaly	***36 (2.7)***

Abbreviations: MCA, multiple congenital anomalies; NT, nuchal translucency.

Overall FTAS test performance

The overall FTAS test performance is summarized in Table 5. The group with other findings (n=82) did not affect test performance if excluded (sensitivity 28.1%, positive predictive value 37.0%).

Table 5. Test performance FTAS (*n*=1 313[a])

TP *n*	FP *n*	FN *n*	TN *n*	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+	LR-
537	775	1 164	98 055	31.6 (29.4-33.9)	99.2 (98.9- 99.5)	40.9 (38.6- 43.2)	98.8 (98.7- 99.0)	40.3	0.7

Abbreviations: FTAS, First-trimester anomaly scan; TP, true positive; FP, false positive; FN, false negative; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.
[a]One case was not included in the test performance analyses due to missing data.

I. True positive cases

In total, 40.9% (537/1 312) of the referred cases were true positive including 332 structural anomalies, 117 genetic anomalies, 82 other findings and 6 cases with IUFD (intrauterine fetal demise) at first detailed diagnostic scan. In 50.1% (266/531), termination of pregnancy (TOP) was done, due to structural or chromosomal anomalies or other findings.

a. Structural anomalies

Table 6 presents an overview of the structural anomalies (n=332). Diagnostic genetic testing or NIPT after referral was performed in 63.9% (212/332). The predominant structural anomalies were multiple congenital anomalies (21.7%, n=72) and heart defects (19.9%, n=66) with the largest proportion being anomalies resulting in abnormal four-chamber view (n=36). The median time to diagnosis for structural anomalies was 20 days (6-43 days) at a median GA of 16+3 weeks (14+4–19+6 weeks). 49.4% (n=164) resulted in TOP, 6.6% (n=22) in IUFD and 42.8% (n=142) in live births.

b. Genetic anomalies

The detected genetic anomalies (n=117) are shown in Table 7. The most frequent finding was trisomy 21 (38.5%, n=45). Overall, the median time to diagnosis was 17 days (8.5-27.5 days) at a median GA of 15+6 weeks (14+6–17+3 weeks). Most pregnancies (82.9%, n=97) resulted in TOP, with 9.4% (n=11) resulting in IUFD and only 7.7% (n=9) in live births.

Table 6. Structural anomalies (*n*=332)

Structural anomaly	Total *n*	Time to diagnosis (days after referral) Median (IQR)	GA at moment of diagnosis (weeks+ days) Median (IQR)	Pregnancy outcome			
				Live birth *n*	TOP *n*	IUFD *n*	Other/ Unknown *n*
Central nervous system	***36***	***7.5 (3-18)***	***14+5 (13+6-16+2)***	***3***	***31***	***0***	***2***
Spina bifida	18	9 (3.8-27.5)	15+2 (14+0-17+4)	3	14	0	1
Anencephaly	8	3.5 (2-7.3)	14+1 (13+4-14+5)	0	7	0	1
Holoprosencephaly (unspecified)	4	5.5 (0-9.5)	14+2 (13+3-14+6)	0	4	0	0
Encephalocele	2	5	14+1	0	2	0	0
Posterior fossa anomaly[a]	2	22.5	16+6	0	2	0	0
Intracranial cyst	1	54	21+0	0	1	0	0
Multiple intracranial anomalies[b]	1	34	17+6	0	1	0	0
Corpus callosum agenesis	0	-	-	0	0	0	0
Hydrocephalus	0	-	-	0	0	0	0
Other	0	-	-	0	0	0	0
Face	***19***	***35 (15-42)***	***18+5 (16+2-19+3)***	***12***	***6***	***1***	***0***
Cleft lip and/or palate	13	29 (12-42)	17+5 (15+1-19+5)	8	4	1	0
Retrognathia/micrognathia	5	37 (26-44)	18+6 (17+4-19+6)	4	1	0	0
Other[c]	1	20	16+2	0	1	0	0
Neck	***0***	***-***	***-***	***0***	***0***	***0***	***0***
Thorax/lungs	***12***	***32 (3.8-57)***	***18+3 (14+1-21+0)***	***5***	***5***	***1***	***1***
Diaphragmatic hernia	9	12 (2-45)	15+0 (14+0-20+0)	2	5	1	1
Pulmonary anomalies[d]	3	60	22+4	3	0	0	0
Heart	***66***	***27.5 (6-49)***	***17+4 (14+6-20+4)***	***32***	***34***	***0***	***0***
Anomalies resulting in abnormal 4CV[e]	36	15.5 (5-41)	15+5 (14+5-19+3)	6	30	0	0
Complex heart defect	5	35 (3-66.5)	19+1 (14+3-23+0)	3	2	0	0
Outflow tract anomalies[f]	9	30 (10.5-56)	17+4 (15+1-21+5)	7	2	0	0
Septal defect[g]	6	43 (5.8-56.8)	19+5 (13+6-21+5)	6	0	0	0
Minor CHD[h]	10	43 (41.8-50.8)	20+0 (19+3-20+4)	10	0	0	0
Abdomen	***36***	***36.5 (8-45)***	***18+5 (14+5-19+5)***	***27***	***9***	***0***	***0***

Table 6. (Continued)

Structural anomaly	Total *n*	Time to diagnosis (days after referral) Median (IQR)	GA at moment of diagnosis (weeks+ days) Median (IQR)	Pregnancy outcome			
Gastroschisis	18	15.5 (7.3-40)	15+4 (14+6-19+0)	14	4	0	0
Omphalocele	7	11 (6-48)	14+2 (13+5-20+2)	2	5	0	0
Intra-abdominal cyst	6	44.5 (36.8-51.5)	19+5 (19+0-21+2)	6	0	0	0
Esophageal atresia	1	1	13+4	1	0	0	0
Abnormal anatomy umbilical vein[i]	2	42	19+4	2	0	0	0
Intra-abdominal echogenicity[j]	1	46	19+5	1	0	0	0
Intestinal anomaly[k]	1	37	19+3	1	0	0	0
Gallbladder anomaly	0	-	-	0	0	0	0
Urogenital system	***34***	***39 (20-50.5)***	***19+3 (16+3-20+6)***	***21***	***9***	***3***	***0***
Bladder / urethral anomaly[l]	12	24 (6.8-48.8)	16+6 (14+4-20+3)	4	6	2	0
Hydronephrosis	9	41 (36.5-46)	19+3 (19+0-20+4)	9	0	0	0
Multicystic or polycystic dysplastic kidney(s)	4	48 (40-68.8)	20+5 (19+0-23+3)	3	1	0	0
Renal agenesis	3	8	14+5	1	2	0	0
Ureteral duplication	2	45.5	20+1	2	0	0	0
Genital anomaly[m]	2	68	22+4	1	0	1	0
Pelvic kidney / horseshoe kidney / unilocular cyst	2	26	17+6	2	0	0	0
Skeletal	***14***	***42.5 (7.5-58)***	***19+6 (14+4-22+3)***	***9***	***4***	***1***	***0***
Skeletal dysplasia	5	3 (1.5-36.5)	14+4 (14+3-18+5)	1	4	0	0
Hemivertebra	3	56	22+0	3	0	0	0
Sacrococcygeal teratoma	1	71	23+1	1	0	0	0
Craniosynostosis	0	-	-	0	0	0	0
Pectus excavatum	0	-	-	0	0	0	0
Other[n]	5	42 (37-50)	19+4 (18+6-21+2)	4	0	1	0

Table 6. (Continued)

Structural anomaly	Total *n*	Time to diagnosis (days after referral) Median (IQR)	GA at moment of diagnosis (weeks+ days) Median (IQR)	Pregnancy outcome			
Extremities	***36***	***36.5 (11.3-43.8)***	***19+2 (15+2-19+6)***	***24***	***10***	***1***	***1***
Club foot	17	38 (27.5-46)	19+4 (17+1-19+6)	16	1	0	0
Limb deformities	9	15 (6-31.5)	15+3 (14+5-18+4)	4	5	0	0
Deformities of hand/fingers/toes	7	45 (34-52)	19+5 (18+0-21+1)	4	2	0	1
Abnormal limb position (excl. pes equinovarus)[o]	3	10	15+2	0	2	1	0
Other	0	-	-	0	0	0	0
Hydrops/ascites	***7***	***10 (5-14)***	***14+5 (14+0-16+1)***	***0***	***5***	***2***	***0***
MCA	***72***	***11 (5-29.5)***	***15+1 (14+1-17+6)***	***8***	***51***	***13***	***0***
Total	**332 (100%)**	**20 (6-43)**	**16+3 (14+4-19+6)**	**142 (42.8%)**	**164 (49.4%)**	**22 (6.6%)**	**4 (1.2%)**

Results of diagnostic genetic testing (GA <24 weeks) were normal or diagnostic genetic testing was not performed.
Abbreviations: IQR, Interquartile Range; GA, Gestational age; TOP, Termination of Pregnancy; IUFD, Intrauterine Fetal Demise; 4CV, four-chamber view; MCA, multiple congenital anomalies.
[a]Fossa posterior anomaly (incl. cerebellar anomalies): Dandy-Walker syndrome.
[b]Multiple intracranial anomalies: e.g. abnormal posterior fossa, corpus callous agenesis, ventriculomegaly.
[c]Face other: malformation of the nose with nasal cyst.
[d]Pulmonary anomalies: Congenital pulmonary airway malformation (CPAM), hydrothorax.
[e]Anomalies resulting in abnormal four-chamber view: hypoplastic left heart syndrome (HLHS), hypoplastic right heart syndrome (HRHS), Ebstein, tricuspid dysplasia, unbalanced atrioventricular septal defect (AVSD).
[f]Outflow tract anomalies: Tetralogy of Fallot, transposition of the great arteries (TGA), aortic arch anomalies
[g]Septal defects: balanced AVSD, ventricular septal defect(s) (VSD).
[h]Minor congenital heart disease (CHD): left/right disproportion, isolated cardiac malposition, cardiomegaly, pericardial effusion, situs inversus totalis.
[i]Abnormal anatomy umbilical vain: PRUV.
[j]Echogenic focus: liver calcifications.
[k]Intestinal anomaly: e.g. right-sided enlarged stomach
[l]Bladder / urethral anomaly: lower urinary tract obstruction (LUTO), urethral valves, megalourethra, urachal cyst
[m]Genital anomaly: hypospadias.
[n]Skeletal other: scoliosis, (extra) fetal structure, sacral dimple.
[o]Abnormal limb position (excl. pes equinovarus): arthrogryposis, abnormal position of hands and/or feet.

Table 7. Genetic anomalies (*n*=117)

Genetic anomaly	Total *n* (%)	Anomalies at first detailed diagnostic scan	Time to diagnosis (days after referral) Median (IQR)	GA at moment of diagnosis (weeks+ days) Median (IQR)	Pregnancy outcome			
					Live birth *n*	TOP *n*	IUFD *n*	Other/ Unknown *n*
Trisomy 21	45 (38.5)	Increased NT (n=13); Increased NT, cardiac defect (n=5); Increased NT, sonomarker(s) (n=7); Increased NT, sonomarker(s), cardiac defect (n=3); MCA (n=4); Hydrops (n=4); Hydrops, sonomarker(s) (n=2); Increased NT, sonomarker(s), other defect (n=2); Cardiac defect, sonomarker(s) (n=2); Increased NT, sonomarker(s), FGR (n=1); Lateral neck cyst (n=1); Cardiac defect (n=1)	15 (8.5-28.5)	15+4 (14+4-17+2)	4	39	2	0
Triploidy	20 (17.1)	MCA (n=17); FGR (n=3)	9.5 (8-16.8)	15+3 (14+4-16+0)	0	16	4	0
Monosomy X	10 (8.5)	Hydrops (n=5); Increased NT (n=2); MCA (n=2); Increased NT, cardiac defect (n=1)	7.5 (4.8-19.3)	14+6 (14+1-16+5)	1	8	1	0
Trisomy 18	8 (6.8)	MCA (n=5); Increased NT, cardiac defect (n=1); Omphalocele, sonomarker(s) (n=1), Hydrops (n=1)	9 (5.3-11.8)	14+4 (13+6-15+3)	0	6	2	0
Trisomy 13	4 (3.4)	MCA (n=4)	7 (1-14.5)	15+1 (13+5-16+2)	0	3	1	0
Other[a]	30 (25.6)	MCA (n=9); Cardiac defect (n=4); Skeletal dysplasia (n=5); Facial (n=2); Increased NT (n=1); Increased NT, cardiac defect (n=1); Distended bowel (n=1); FGR (n=1); FGR, sonomarker(s), intra-abdominal cyst (n=1); Hydrops (n=2); Increased NT, sonomarker(s), mild frontal bossing (n=1); Lateral neck cyst (n=1); Pes equinovarus (n=1)	27.5 (24.8-45.5)	18+0 (16+4-20-1)	4	25	1	0
Total	**117 (100)**		**17 (8.5-27.5)**	**15+6 (14+6-17+3)**	**9 (7.7%)**	**97 (82.9%)**	**11 (9.4%)**	**0 (0.0%)**

Diagnostic genetic testing (GA <24 weeks) and/or NIPT was performed after referral.
Abbreviations: IQR, Interquartile Range; GA, Gestational age; TOP, Termination of pregnancy; IUFD, Intrauterine fetal demise; NT, Nuchal translucency; MCA, Multiple congenital anomalies; FGR, Fetal growth restriction; SUA, Single umbilical artery.
[a]Other: Homozygous CRTAP mutation (*n=1);* ANKRD11 mutation associated with KBG syndrome (*n=1);* FLT4 mutation associated with Milroy disease (*n=2);* CTNND1 mutation (*n=1);* CDK 10 mutation (*n=1);* FGFR3 mutation (*n=1);* Loss 15.8Mb; 9p24.3p22.3 (*n=1);* Type I NF1 microdeletion (*n=1);* AP4B1 mutation (*n=1);* FOXH1 mutation (*n=1);* Loss 10.6 Mb; 3p26.3p25.3, gain 3.8 Mb; 17p13.3p13.2, high gain 652 kb; 17p13.2, gain 1.4 Mb; 17q12 (*n=1);* Gain 115 kb; 17p13.3 (*n=1);* ETCC2 mutation (*n=1);* Mosaic trisomy 15 (*n=1);* COL1A1 mutation (*n=1);* Wolf-Hirschhorn syndrome (*n=1);* Trisomy 9 (*n=1);* 22q11.21 mutation (*n=1);* MYH6 mutation (*n=1);* 11q12 mutation associated with BCD syndrome type 2 (*n=1);* CDC42BPB mutation (*n=1);* 12q21 deletion syndrome (*n=1);* COL1A2 mutation (*n=1);* NEK9 mutation (*n=1);* Heterozygous for the variant c.1403C>G, p.(Ser468*) in PPM1D (*n=1);* Heterozygous for the variant c.762+1del p.(?) in COL2A1 (*n=1);* Trisomy 18 and Klinefelter syndrome (48,XXY,+18) (*n=1);* Homozygous for the variant c.1868-1G>T p.(?) in PLD1 (*n=1).*

c. Other findings

Table 8 presents various other findings. The majority were sonomarkers (42.7%, n=35) and abnormal fetal biometry (41.5%, n=34). 6.1% (n=5) resulted in TOP, 11.0% (n=9) in IUFD, 82.9% (n=68) in live births.

Table 8. Other findings (*n*=82)

Finding	Total *n* (%)	Pregnancy outcome			
		Live birth *n*	TOP *n*	IUFD *n*	Other/ Unknown *n*
Sonomarker	35 (42.7)	34	1	0	0
Abnormal fetal biometry	34 (41.5)	23	3	8	0
Placental/umbilical cord anomaly[a]	11 (13.4)	11	0	0	0
An-/oligohydramnios	2 (2.4)	0	1	1	0
Total (%)	**82 (100)**	**68 (82.9)**	**5 (6.1)**	**9 (11.0)**	**0 (0.0)**

Abbreviations: TOP, Termination of Pregnancy; IUFD, Intrauterine Fetal Demise.
[a]Placental/umbilical cord anomaly: e.g. umbilical cord cysts, circumvallate placenta.

II. False positive cases

In total, 59.1% (775/1 312) of the referrals turned out to be normal. Of these, 586 had a normal first detailed diagnostic scan and 189 had anomalies that were observed on the FTAS and first detailed diagnostic scan, but which resolved before 24 weeks GA, defining them as transient findings. This resulted in a false-positive rate of 0.8% (775/98 830). In cases with a normal first detailed diagnostic scan (n=586), the majority were referred because of abnormal fetal biometry (42.8%, n=251) or a structural anomaly (38.6%, n=226). The predominant ultrasound anomalies observed in cases with transient findings (Table A.4.) comprised increased nuchal translucency (n=52), abnormal fetal biometry (n=47) and distended jugular sacs (n=17). Of cases with transient findings, 0.5% (n=1) resulted in IUFD and 98.4% (n=186) in live births. In 9 cases (4.8%), anomalies were present after birth.

III. False negative cases

In total, of the 127 979 cases with a normal or incomplete FTAS result, 1 164 (0.9%) had an anomaly detected during the SAS, resulting in a false negative rate of 68.4% (1 164/1 701) for the FTAS. Structural anomalies were diagnosed in 92.4% (n=1 076) and genetic anomalies in 6.9% (n=80). Of the structural anomalies, most were heart defects (24.9%, n=268) with a significant proportion being outflow tract anomalies (n=148) followed by septal defects (n=62). In addition, anomalies of the urogenital system (n=24.3%, n=262)

were frequently diagnosed, largely consisting of ureteral duplication (n=70), pelvic/horseshoe kidney/unilocular cyst (n=52) and hydronephrosis (n=51).

First-trimester major congenital anomalies

Sensitivity for first-trimester major congenital anomalies was 84.6% (126/149). These were found in 126 cases, derived from 96 cases with a structural anomaly and 30 cases with a genetic anomaly (Figure 2). Furthermore, four cases of megacystis resolved spontaneously and one false positive case of gastroschisis was found. In total, 23 first-trimester major congenital anomalies were not detected during the FTAS, but at the SAS, resulting in a false negative rate of 15.4% (23/120). The negative predictive value was 99.9% (CI 99.9%-99.9%). Median time to diagnosis was 9 days (5-22 days) at a median GA of 14+6 weeks (14+1–16+5 weeks).

COMMENT

Principal findings

FTAS in the Netherlands had an uptake of 74.9% with a sensitivity of 84.6% for first-trimester major congenital anomalies and 31.6% for all anomalies combined. This was accompanied by a referral rate of 1.0%, of which 59.1% involved cases where anomalies were either not confirmed at the first detailed diagnostic scan or resolved in the second trimester. Timing of diagnosis was around 16 weeks gestation for referred cases.

Results in the context of what is known

This is the first multicenter study to describe the performance of an FTAS conducted in a nationwide prenatal screening program. All scans were conducted in a low-risk population, using a standardized screening protocol, and not in the context of a nuchal translucency scan. Our sensitivity of 31.6% for the detection of all anomalies is in line with the 32.4% sensitivity in low-risk populations as reported by Karim et al.[4], who reviewed cohort studies including 97 976 fetuses, predominantly conducted in secondary or tertiary care settings. In contrast with the study of Grande et al,[11] in which 13 723 FTAS were performed with a 49% sensitivity for major anomalies, we found a significantly higher sensitivity of 84.6%. Another recent study including 303 319 fetuses, reported a sensitivity of 91.3% in detecting lethal anomalies.[12] The differences in sensitivity are in part explained by the definition of major anomalies which varied considerably among these studies. There is a wide range of detection rates during the first trimester when considering specific anomalies.[3,11,13,14] For anomalies as anencephaly, (alobar) holoprosencephaly and megacystis, a 100% detection rate in the first trimester is reported.[13,15] Therefore, results on FTAS performance may be affected by decisions

regarding classification of anomalies and methodology used for calculation. Of note in our study are the low number of cases with, for example, anencephaly, abdominal wall defects and twin reversed arterial perfusion. It is likely that a proportion of these first-trimester major congenital anomalies could have already been detected at the dating scan, a routine scan in obstetric care in the Netherlands.

We further found that the final prenatal diagnosis was at a median GA of 16+1 weeks for cases with a structural or genetic anomaly. A potential benefit of the FTAS is that it allows parents to have additional time for diagnostic testing and making an informed decision about their pregnancy, as there are weeks remaining before reaching the upper limit (GA 24 weeks) for TOP in the Netherlands. Furthermore, It has been suggested that TOP at an earlier GA is associated with lower levels of grief and posttraumatic stress.[16,17] In our study, 50.1% of pregnancies with an anomaly resulted in TOP at a median GA of 16+1 weeks. The psychological impact of TOP after the FTAS compared to midgestational TOP will be further examined. Another study described that the final diagnosis of structural anomalies detected during the FTAS was reached within the (late) first trimester in 91.7% (11/12) of pregnancies.[18] However, the study defined the moment of diagnosis as the first diagnostic scan where the anomaly was seen, without considering that in many cases a clear prognosis cannot be provided after the initial scan. Further testing, such as genetic testing, follow-up scans and counseling sessions, is often necessary.

In contrast to our study, Kenkhuis et al. reported a lower false positive rate (0.1%) in women opting for the combined test and receiving a detailed anomaly scan following a structured protocol (GA 11+0-13+6 weeks).[14] This lower rate could be attributed to a different setting; exclusion of increased nuchal translucency cases and variation in the calculation of false positive rate, as in the study there were no referrals for abnormal biometry. In our study, cases with resolved increased nuchal translucency (n=52) were considered as false-positives, which is debatable since an increased nuchal translucency is a marker for underlying abnormalities. However, excluding these cases would only slightly affect the false-positive rate (0.7%). Anomalies were either not confirmed or resolved before 24 weeks GA in more than half of the referrals. In a screening setting, it is favorable for sonographers to maintain a low threshold for referring cases to a tertiary care center. However, unnecessary referrals could cause a period of uncertainty and distress for parents. An initial increase of anxiety levels is reported after an abnormal anomaly scan as part of the combined test, but these levels have been described to decrease after a normal SAS.[19] Furthermore, a low referral threshold might cause elevated healthcare costs. It is uncertain whether there will be an improvement in FTAS performance due to a learning curve, potentially reducing the number of false positives. It needs to be considered whether fetal biometry as part of the FTAS

screening protocol provides sufficient benefits for detecting anomalies. Furthermore, it could be deliberated to perform NIPT prior to the FTAS to reduce unnecessary referrals. Another possible disadvantage of the FTAS could be false reassurance of parents due to undetected anomalies. There is no literature yet reporting on the false negative rate of the FTAS. The specific types of undetected anomalies at the FTAS should therefore be further examined.

The setting of our study differs from settings in some other countries where private practice and varying screening uptake might lead to different test performance.[20] Furthermore, it is uncertain how findings of this study can be extrapolated to societies where BMI is much higher. However, this nationwide study could provide valuable insights into the test characteristics of the FTAS in a more standardized and widely applicable context.

Clinical Implications

Our study shows that the FTAS, as part of the nationwide prenatal screening program in the Netherlands, has a high sensitivity in detecting first-trimester major congenital anomalies. For all anomalies combined, a lower sensitivity was found. Earlier diagnosis of fetal anomalies will offer pregnant women and their partners more time for reproductive decision-making and if desired, a TOP earlier in pregnancy.

Research Implications

It should be further studied whether the dating scan, conducted without a structured protocol and the FTAS, performed with a structured protocol, impact the detection of each other. Additionally, further study is needed to determine the optimal timing for the FTAS. Finally, in an exploration of the yield of the FTAS, perspectives of women and healthcare professionals on the FTAS are of pivotal importance.

Strengths and Limitations

In this study, we used unique data of a large nationwide cohort of pregnant women opting for the FTAS. Due to national referral agreements, our study experienced minimal missing data of referred cases. Another strength is that the FTAS was performed by certified and trained sonographers using a uniform protocol. The exclusion of women with a high risk for fetal anomalies minimized bias in the study and strengthened the low-risk population.

A higher or lower nationwide NIPT uptake could have influenced the total number of anomalies detected by the FTAS. Cases with other findings were not included in the total number of false-negatives, which would have caused lower sensitivity and

negative predictive value. Furthermore, we could not report on the presence of fetal anomalies after birth, because no reliable registration of these anomalies is available in our country. Therefore, the second-trimester diagnosis served as the golden standard compared to the FTAS. However, this is defensible, because it is unlikely that the FTAS can detect anomalies that are not observed on the SAS.

CONCLUSIONS

The performance of a newly introduced nationwide FTAS in a low-risk population showed a high sensitivity for first-trimester major congenital anomalies and a lower sensitivity for all anomalies combined. The program was accompanied by a referral rate of 1.0%, of which 59.1% involved cases where anomalies were either not confirmed or resolved before 24 weeks gestation. Timing of diagnosis was around 16 weeks gestation for referred cases. To evaluate the balance between benefits and potential harm of the FTAS within a nationwide prenatal screening program, it is essential to assess the effectiveness of the program over time and to consider the perspectives of both women and their partners, as well as healthcare professionals.

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SUPPLEMENTARY MATERIAL

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Table A.1. Definition moment of final prenatal diagnosis

Situation	
TOP	**Ongoing pregnancy** *The subsequent method for defining follows a hierarchical order.*
When parents opted for TOP, the moment of final prenatal diagnosis was calculated as the date of TOP minus five days (reflection period), based on the assumption that the decision for TOP until the moment of termination is on average five days.	If parents received an abnormal genetic test result, this moment was chosen as the moment of final prenatal diagnosis. In this situation, we expected that parents were provided with sufficient information on the prenatal diagnosis and prognosis to make a reproductive choice regarding their pregnancy.
	In case IUFD had occurred <24 weeks GA, this moment was chosen as the moment of final prenatal diagnosis.
	If the EPF indicated that parents made a reproductive decision about their pregnancy, regardless of following subsequent investigations, this moment was chosen as the moment of final prenatal diagnosis, as more knowledge on the prenatal diagnosis or prognosis was not required for parents to make a reproductive choice.
	If the EPF reported that parents or the maternal-fetal medicine specialist needed other specialists for additional information or counseling (e.g. clinical geneticist, pediatric surgeon) for sufficient knowledge on the diagnosis or prognosis, this moment was stated as the moment of final prenatal diagnosis.
	Some anomalies had a frequent occurrence. In case the above mentioned conditions were not met and the fetus had a clubfoot, the date of the first detailed diagnostic scan in which sufficient visibility about all other organs and other structures (especially the fetal heart) was obtained, was chosen as the moment of final prenatal diagnosis. In this situation, we expected that parents were provided with sufficient information on the prenatal diagnosis and prognosis to make a reproductive choice regarding their pregnancy.
	In case the EPF stated that findings were uncertain (either with normal or absent genetic test results) and/or the EPF did not indicate a reproductive choice of parents, the date of the detailed diagnostic scan <24 weeks was chosen as the moment of final prenatal diagnosis, as this correspond with the upper limit for TOP in the Netherlands.

Abbreviations: TOP, termination of pregnancy; IUFD, intrauterine fetal demise; GA, gestational age; EPF, electronic patient file.

Table A.2. Subgroup analysis baseline characteristics

Characteristics	**FTAS normal** *n*=118 298	**FTAS abnormal** *n*=1 676	**P-value**
Maternal age, years (mean ± SD)[a]	30.8±4.5	31.3±4.8	<0.001
BMI (median, IQR)[b]	23.8 (5.8)	24.0 (6.2)	0.123
Parity, n (%)[c]			0.048
0	53 648 (46.9)	719 (44.4)	
≥1	60 714 (53.1)	899 (55.6)	
Singleton pregnancy, n (%)	116 900 (98.8)	1 608 (95.9)	<0.001
GA at FTAS (weeks), n (%)[d]			0.022
12+1 – 12+2	195 (0.2)	4 (0.2)	
12+3 – 13+0	23 048 (20.1)	360 (22.2)	
13+1 – 13+5	55 706 (48.5)	721 (44.5)	
13+6 – 14+3	34 504 (30.1)	517 (31.9)	
14+4 – 14+5	1 323 (1.2)	20 (1.2)	
NIPT performed, n (%)	82 024 (69.3)	1 063 (63.4)	<0.001

Abbreviations: BMI, Body Mass Index; IQR, Interquartile Range; GA, Gestational Age; FTAS, First-trimester anomaly scan; NIPT, Non-Invasive Prenatal Testing.
[a]Maternal age: missing 60
[b]BMI: missing 6 979
[c]Parity: missing 3 994
[d]GA at FTAS: missing 3 576

Table A.4. Transient ultrasound findings (*n*=189)

Findings at first detailed diagnostic scan	**Total *n* (%)**
Structural anomaly	***69 (36.5)***
Central nervous system	*6 (8.7)*
Spina bifida	0 (0.0)
Anencephaly	0 (0.0)
Holoprosencephaly (unspecified)	0 (0.0)
Encephalocele	0 (0.0)
Posterior fossa anomaly	0 (0.0)
Intracranial cyst	2 (33.3)
Multiple intracranial anomalies	0 (0.0)
Corpus callosum agenesis	0 (0.0)
Hydrocephalus	0 (0.0)
Other[a]	4 (66.7)
Face	*5 (7.2)*
Cleft lip and/or palate	1 (20.0)
Retrognathia/micrognathia	4 (80.0)
Neck	*17 (24.6)*
Thorax/lungs	*1 (1.4)*
Diaphragmatic hernia	0 (0.0)
Pulmonary anomalies	1 (100.0)
Heart	*7 (10.1)*
Anomalies resulting in abnormal 4CV	0 (0.0)
Complex heart defect	0 (0.0)
Outflow tract anomalies	0 (0.0)
Septal defect	1 (14.3)
Minor CHD	6 (85.7)
Abdomen	*13 (18.8)*
Gastroschisis	1 (7.7)
Omphalocele	3 (23.1)
Intra-abdominal cyst	6 (46.2)
Esophageal atresia	0 (0.0)
Abnormal anatomy umbilical vein	0 (0.0)
Intra-abdominal echogenicity	3 (23.1)
Intestinal anomaly	0 (0.0)
Gallbladder anomaly	0 (0.0)
Urogenital system	*10 (14.5)*
Bladder / urethral anomaly	4 (40.0)

Table A.4. (Continued)

Findings at first detailed diagnostic scan	**Total *n* (%)**
Hydronephrosis	6 (60.0)
Multicystic or polycystic dysplastic kidney(s)	0 (0.0)
Renal agenesis	0 (0.0)
Ureteral duplication	0 (0.0)
Genital anomaly	0 (0.0)
Pelvic kidney / horseshoe kidney / unilocular cyst	0 (0.0)
Skeletal	*3 (4.3)*
Skeletal dysplasia	0 (0.0)
Hemivertebra	0 (0.0)
Sacrococcygeal teratoma	0 (0.0)
Craniosynostosis	0 (0.0)
Pectus excavatum	0 (0.0)
Other[b]	3 (100.0)
Extremities	*3 (4.3)*
Club foot	3 (100.0)
Limb deformities	0 (0.0)
Deformities of hand/fingers/toes	0 (0.0)
Abnormal limb position (excl. pes equinovarus)[o]	0 (0.0)
Other	0 (0.0)
Hydrops/ascites	*0 (0.0)*
MCA	*4 (5.8)*
Sonomarker	***63 (33.3)***
Increased NT (≥3.5mm)	52 (82.5)
Hypoplasia/aplasia nasal bone	2 (3.2)
Echogenic bowel	2 (3.2)
Choroid plexus cyst	2 (3.2)
Single umbilical artery	2 (3.2)
≥2 sonomarkers	3 (4.8)
Cardiac echogenic focus	0 (0.0)
Abnormal fetal biometry	***47 (24.9)***
Placental/umbilical cord/amniotic fluid anomaly	***10 (5.3)***

Abbreviations: MCA, multiple congenital anomalies; NT, nuchal translucency.
[a]Central nervous system other: abnormal cerebral cortex, abnormal thalamus, ventriculomegaly
[b]Skeletal other: abnormal spine, echogenicity caput