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Prenatal diagnosis and pregnancy outcome of major structural anomalies detectable in the first trimester: A population-based cohort study in the Netherlands

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Abstract

Background: Prenatal diagnosis of several major congenital anomalies can be achieved in the first trimester of pregnancy.

Objective: This study investigates the timing of diagnosis and pregnancy outcome of foetuses and neonates with selected structural anomalies in the Northern Netherlands over a 10-year period when the prenatal screening programme changed significantly, but no first-trimester anatomical screening was implemented.

Methods: We performed a population-based retrospective cohort study with data from the EUROCAT Northern Netherlands database on pregnancies with delivery or termination of pregnancy for fetal anomaly (TOPFA) date between 2010 and 2019. The analysis was restricted to anomalies potentially detectable in the first trimester of pregnancy in at least 50% of cases, based on previously published data. These included: anencephaly, encephalocele, spina bifida, holoprosencephaly, tricuspid/pulmonary valve atresia, hypoplastic left heart, abdominal wall and limb reduction defects, lethal skeletal dysplasia, megacystis, multiple congenital anomalies. The primary outcome was the timing of diagnosis of each structural anomaly. Information on additional investigations, genetic testing and pregnancy outcome (live birth, TOPFA and foetal/neonatal death) was also collected.

Results: A total of 478 foetuses were included; 95.0% (n = 454) of anomalies were detected prenatally and 5.0% (n = 24) postpartum. Among the prenatally detected cases, 31% (n = 141) were diagnosed before 14 weeks of gestation, 65.6% (n = 298) between 14–22 weeks and 3.3% (n = 15) after 22 weeks. Prenatal genetic testing was performed in 80.4% (n = 365) of cases with prenatally diagnosed anomalies, and the results were abnormal in 26% (n = 95). Twenty-one% (n = 102) of pregnancies resulted in live births and 62.8% (n = 300) in TOPFA. Spontaneous death occurred in 15.9% (n = 76) of cases: in-utero (6.1%, n = 29), at delivery (7.7%, n = 37) or in neonatal life (2.1%, n = 10).

Conclusion: Major structural anomalies amenable to early diagnosis in the first trimester of pregnancy are mostly diagnosed during the second trimester in the absence of a regulated first-trimester anatomical screening programme in the Netherlands and are associated with TOPFA and spontaneous death, especially in cases with underlying genetic anomalies.

KEYWORDS
congenital anomalies, prenatal diagnosis, prenatal screening

1 | BACKGROUND

Congenital anomalies affect about 2–3% of newborns and represent important causes of infant death, chronic illness and long-term disability.[1,2] Although very heterogeneous in nature and presentation, congenital anomalies may significantly benefit from early diagnosis.[3] With advances in prenatal screening (PNS) and invasive testing, a substantial proportion of congenital anomalies can now be accurately identified during pregnancy.[4,5] Early diagnosis is essential for the organisation of perinatal and postnatal care and offers more time for additional investigations and counselling on the implications, prognosis and expected outcome of the pregnancy. At this point treatment options and, when legally allowed, termination of pregnancy for fetal anomaly (TOPFA) can be discussed with parents. A recent large multicentre study has demonstrated a negative association between TOPFA prevalence and perinatal mortality among cases of children with congenital anomalies, with TOPFA rates accounting for a significant proportion of between-country variation in perinatal mortality among affected babies.[6]

The first step towards the prompt diagnosis of congenital anomalies is prenatal screening PNS. In the Netherlands, PNS was introduced in 2007 with the implementation of second-trimester anatomical screening (STAS) and the first-trimester combined test (CT).[7,8] Meanwhile, advances in ultrasound and genetic technology have allowed for even earlier detection of a number of congenital defects. Indeed, by now, the role of the first-trimester anatomical screening (FTAS) is well established, and FTAS has been introduced in the national screening programmes of several European countries.[9–13] In the Netherlands, FTAS is offered since September 2021.[14] Previously, anatomical assessment took place during STAS. However, some anomalies which are evident on ultrasound were detected during crown-rump length (CRL) measurement ('dating scan') at 10 weeks of gestation or the nuchal translucency (NT) scan as part of the CT. Because FTAS was not yet part of the national screening programme, an increasing number of women opted for an early scan in private ultrasound practices at own costs. Although structural anomalies were occasionally detected during these scans, sonographers were not required to meet quality standards nor to participate in a national audit.

Anomalies amenable to first-trimester diagnosis account for about 30% of all prenatally detectable defects and include most neural tube and abdominal wall defects, megacystis, as well as selected severe cases of skeletal and cardiac anomalies.[15–17] In light of the recent introduction of FTAS in the Netherlands as additional screening moment for structural anomalies, and in order to study the added value of this early scan, it is relevant to analyse the timing of prenatal diagnosis of structural anomalies potentially amenable to early diagnosis. This study aims to do so by using the European Surveillance of Congenital Anomalies registry (EUROCAT) of the Northern Netherlands in a 10-year period preceding the introduction of FTAS and in which the prenatal screening programme was subject to various changes. Secondly, it also evaluates pregnancy outcome in these foetuses.

Synopsis

Study Question

When are structural anomalies that are potentially detectable in the first trimester of pregnancy diagnosed in foetuses when no regulated first-trimester anatomical screening is performed?

What is the pregnancy outcome of these cases?

What's Already Known

About 30% of congenital anomalies can be diagnosed by ultrasound during the first trimester of pregnancy.

Major structural anomalies are associated with high rates of termination of pregnancy.

What this Study Adds

Major structural anomalies amenable to early diagnosis in the first trimester of pregnancy are mostly diagnosed during the second trimester in the absence of a regulated first-trimester anatomical screening programme and are associated with high rates of termination of pregnancy for fetal anomaly (TOPFA) and spontaneous death, especially in cases with underlying genetic anomalies.

2 | METHODS

2.1 | History of prenatal screening in the Netherlands

Prenatal screening was introduced in the Netherlands in 2007. The programme included the CT with nuchal translucency measurement, as screening for trisomy 21 and STAS for structural anomalies. In 2010, the screening coverage of the CT was expanded to trisomy 13 and trisomy 18. In 2014, non-invasive prenatal testing (NIPT) by cell-free DNA (cfDNA) was introduced for women with a high risk at the CT, defined as >1:200. At the time, NIPT was only used to screen for trisomy 21, 18 and 13. However, since 2017 NIPT is offered universally to all women, who can also opt for genome-wide cfDNA screening. The most recent change in the prenatal screening programme was the introduction of FTAS in research setting from September 2021.

2.2 | Study design and setting

We performed a population-based retrospective cohort study with data extracted from the EUROCAT Northern Netherlands (NNL) database; a population-based registry gathering data from foetuses and children with congenital anomalies in the three northern provinces of the Netherlands (Groningen, Friesland and Drenthe). The EUROCAT-NNL registry started in 1981 and after gradually extending the covered region, it now covers all cases of live births, foetal deaths and TOPFA in the region.[18] Nowadays, this accounts for approximately 15,500 births per year, which corresponds to circa 10% of all births in the Netherlands. There is no lower limit for gestational age and data are continuously updated in the register until the completed 10th year of age of the child, which corresponds to the upper limit for inclusion in the data set. The database reports on all types of congenital abnormalities, including major structural malformations (and if concurrently present also minor), chromosomal anomalies and single-gene disorders. Data registry is monitored by quality control indicators and is based on multiple sources of ascertainment.[19] These include prenatal and postnatal patient records, pregnancy outcome and delivery reports, cytogenetic laboratory investigations and postmortem examinations. Cases are registered in the database after parental consent and are coded according to the 10th revision of the International Classification of Diseases (ICD) with the British Paediatric Association extension code (ICD10/BPA). When parents do not respond to several requests for case registration, they are coded as 'non-responders'. These cases are included in the database, but with limited information ('core variables'), including diagnosis and pregnancy outcome. Non-responders were 24% of cases included in our cohort. Only when parents actively refuse registration, cases are not included in the database. This happened in 6.6% of cases in the study period. For all cases included, available information on additional ultrasound scans, invasive testing and genetic diagnosis during pregnancy and postpartum was collected. Pregnancy outcome (live birth, foetal death, TOPFA, stillbirth and neonatal death), gestational age at delivery and birth weight were recorded as well. In the Netherlands, TOPFA is allowed until 24 weeks of gestation. After that, it is offered to parents only in case of lethal foetal anomalies.

2.3 | Cohort

The study population consisted of all foetuses and newborns diagnosed with at least one of a selected group of structural anomalies, recorded in the EUROCAT-NNL database and with delivery/TOPFA date between 1–1–2010 and 31–12-2019. The selected group of structural anomalies comprised all defects with a first-trimester detection rate of at least 50% reported in the two most recent and largest cohorts on first-trimester detection rates.[15,16] The selected anomalies (with corresponding ICD10 codes) have been grouped according to the affected organs and are described in Table 1. When specific ICD-10 codes were not available, the anomalies were selected based on the broader ICD-10 group with subsequent application of a text filter. These cases are marked in Table 1 as 'subgroup of ICD-10 code.'

Lethal skeletal dysplasia was defined as (genetic) disorders characterised by abnormal growth and development of bone and cartilage which leads to foetal or infant death within the first year of life. Limb reduction defects (LRD) were included when at least one of the following long bones was absent: humerus, ulna, radius, femur, tibia, fibula or absent or when at least one hand or foot was missing. Cases with isolated digital anomalies were not included. Multiple congenital anomalies (MCA) were defined as two or more unrelated structural anomalies (including at least one of the above-specified selected anomalies) in at least two different organ systems. For all responders, we included maternal demographic and obstetric characteristics. For non-responders, these data were not available. Ethnicity was defined as Western and non-Western based on the country of birth of the maternal grandparents. Maternal educational level was classified as low (primary school, lower vocational and prevocational education), middle (secondary vocational education, general secondary education and pre-university education) and high (college or university education) based on the self-reported highest educational level achieved. Gravidity was defined as primigravida and multigravida and parity as no live births, 1 live birth or 2 or more live births.

2.4 | Exclusion criteria

Although atrioventricular septum defects (AVSD) are prenatally detected in the first trimester in at least 50%, we excluded all AVSDs, because in the great majority of cases the diagnoses was made at follow-up scan after a high risk of trisomy 21 at the CT, rather than during STAS.

TABLE 1 Structural anomalies that were included in the study

Anomalies groups	Selected anomalies (ICD code)
Central nervous system anomalies	Anencephaly (Q00) Encephalocele (Q01) Spina bifida (Q05) Holoprosencephaly (Q042)
Congenital heart defects	Hypoplastic left heart syndrome (Q234) Pulmonary valve atresia (Q220) Tricuspid valve atresia (subgroup of Q224)
Abdominal wall defects	Omphalocele (Q792) Gastroschisis (Q793) Pentalogy of Cantrell (subgroup of Q897) Limb–body-wall complex (LBWC) (subgroup of Q795)
Skeletal anomalies	Lethal skeletal dysplasia (subgroup of Q78) • Thanatophoric dysplasia (Q771) • Achondrogenesisis (Q7700, Q7701) • Osteogenesis imperfecta type 2 (Q7800) Limb reduction defects (LRD) (subgroup of Q71-Q72)
Congenital anomalies of kidney and urinary tract (CAKUT)	Megacystis (subgroup of Q6476)
Multiple congenital anomalies	Multiple congenital anomalies (MCA) were defined as two or more unrelated structural anomalies (including at least one of the above-specified selected anomalies) in at least two different organ systems.

2.5 | Outcomes

The primary outcome was the timing of diagnosis of each structural anomaly. When anomalies were prenatally detected, gestational age at diagnosis was recorded and based on this, three groups were made: diagnosis <14 weeks, between 14–22 weeks and >22 weeks. In cases with MCA, we recorded as time of diagnosis the gestational age at which the first anomaly was diagnosed. The secondary outcome was pregnancy outcome. Foetal death was defined a spontaneous foetal death during pregnancy. Death at delivery was defined as spontaneous death which occurred during delivery or within the first 24 h of life. Neonatal death was defined as death occurring within 28 days following delivery of the child. Finally, we assessed the time (in days) between diagnosis and TOPFA for each structural anomaly.

2.6 | Statistical analyses

Normally distributed variables were described by mean (SD), skewed distributions by median (IQR range). Descriptive and comparative analyses were performed in IBM-SPSS Statistics for Windows, version 23.0.0.3 (Armonk, NY: IBM Corp.)

2.7 | Missing data

Data were complete for the primary and secondary outcomes: congenital anomalies and overall diagnosis, year of birth, pregnancy outcome, date of death, gestational age at birth or at TOPFA and (gestational age at) diagnosis. Demographic data were missing for non-responders. For each of those variables, we presented the percentage missing data. Since demographic characteristics were only used to describe the population, no adjustment for missing data was performed.

2.8 | Ethics approval

Due to the retrospective nature of the study, formal approval by the local medical ethical committee was not required. This study was performed with anonymised patient data. The registry operates within the scope of the General Data Protection Regulation (GDPR) and the Code of Good Conduct, set up by the Dutch Federation of Biomedical Scientific Societies. National legislation requires informed consent case registration.

3 | RESULTS

In the study period, 5517 children and foetuses with congenital anomalies were registered in the EUROCAT-NNL database. After application of the inclusion criteria, 478 cases were selected; 362 (75.8%) were responders and 116 were non-responders (24.2%). Maternal demographic and obstetrical characteristics are described in Table 2. Mean maternal age was 30.0 (SD 5.4 years). Among responders, mothers (n = 282/306, 92.2%) were of Western ethnicity and had a middle educational level (140/291, 48.1%). Obstetric characteristics showed that 64.1% (n = 210) of women were multigravidae, 88/290 (30.3%) had a history of miscarriage, 15 (5.2%) of

TOPFA and 3 (1.0%) of stillbirth. Foetal gender was more often male (*n* = 242/262, 52.4%). Median birthweight in live births was 3037 gr (IQR 2555, 3427.5).

Table 3 shows the moment of detection of the selected structural anomalies. In total, 95.0% (*n* = 454) of congenital anomalies were detected prenatally and 5.0% (*n* = 24) postpartum. Among the prenatally detected ones, 31% (*n* = 141) were diagnosed before 14 weeks of gestation, 65.6% (*n* = 298) between 14–22 weeks and 3.3% (*n* = 15) after 22 weeks. With a first-trimester detection rate of 70% (*n* = 7), megacystis was the anomaly most often detected in the first trimester. (Table 3) Next up, we find omphalocele in 69.6% (*n* = 32) of cases, anencephaly in 54.8% (*n* = 34), pentalogy of Cantrell/LBWC in 47.4% (*n* = 9), and MCA in 45.9% (*n* = 28). The remaining cases of CNS anomalies (encephalocele, spina bifida and holoprosencephaly) were mainly detected between 14 and 22 weeks of gestation, together with cardiac and skeletal anomalies. Postnatal diagnosis was the highest for LRD (25.9%, *n* = 7) and skeletal dysplasia (11.1%, *n* = 2). For all other anomalies, postpartum diagnosis was in <10% of cases (range: 0–9.8%).

TABLE 2 Characteristics of the study population

	Total[c] (*n* = 478) *n*	%[b]
Maternal age, years (n = 475/478)		
Mean (SD)	30.0	(5.4)
Missing	*3*	*(0.6)*
Maternal ethnicity (*n* = 306/478)		
Western	282	(92.2)
Non-western	24	(7.8)
Missing	*172*	*(36.8)*
Maternal educational level (*n* = 291/478)		
Low	22	(7.6)
Middle	140	(48.1)
High	129	(44.3)
Missing	*187*	*(39.1)*
Gravidity (*n* = 343/478)		
1	123	(35.9)
>1	220	(64.1)
Missing	*135*	*(28.2)*
Parity (live births only)(*n* = 290/478)		
0	106	(36.6)
1	128	(44.1)
≥2	56	(19.3)
Missing	*188*	*(39.3)*
Obstetrical history (*n* = 106/478)		
Miscarriage	88	(30.5)
TOP	15	(5.2)
Stillbirth	3	(1.0)
Missing	*190*	*(39.7)*
Foetal gender (*n* = 462/478)		
Male	242	(52.4)
Female	220	(47.6)
Unknown[a]	*16*	*(3.4)*
Birthweight in live births, gram (*n* = 146/478)		
Median, IQR	*3037*	(2555.0, 3427.5)
Unknown	*3*	*(2.0)*

[a]Cases with TOPFA or early foetal death in which foetal gender was not macroscopically identifiable by post-mortem examination and in which genetic investigation was not performed.

[b]Demographic information was not available for non-responders, coded as *missing*. The percentages refer to responders only.

[c]The total of 478 cases includes both responders (n = 362) and non-responders (n = 116), now counted in the 'missing' group.

The results of genetic testing performed during pregnancy in foetuses with a prenatally diagnosed structural anomaly are presented in Table 4. Genetic testing was performed in 80.4% (*n* = 365) of cases with a prenatally diagnosed structural defect and was abnormal in 27.7% (*n* = 101). Of all CNS anomalies, holoprosencephaly was the one most frequently associated with an underlying genetic diagnosis in 60% (*n* = 12) of cases. Most cardiac anomalies (86.0%, *n* = 74) did not have a co-existing genetic diagnosis. Among skeletal defects, lethal skeletal dysplasia was associated with a genetic diagnosis in the majority of cases (93.8%, *n* = 15). Genetic anomalies were also diagnosed in 39.8% of abdominal wall defects, and particularly in foetuses with omphalocele (60.9%, *n* = 28). Megacystis was also paired to an underlying genetic cause in more than half of the cases (55.6%, *n* = 5).

Pregnancy outcome is shown in Table 5. In total, 21.3% (*n* = 102) of pregnancies resulted in a live birth and 62.8% (*n* = 300) in TOPFA. Spontaneous death occurred in 15.9% (*n* = 76) of cases: in-utero (6.1%, *n* = 29), at delivery (7.7%, *n* = 37) or in neonatal life (2.1%, *n* = 10). The highest rate of TOPFA was for megacystis (80%, *n* = 8) and CNS anomalies (79.0%, *n* = 128), followed by cardiac defects (56.8%, *n* = 54). Anencephaly was the anomaly with the single highest rate of TOPFA (90.3%, *n* = 56). Limb reduction defects had the highest number of live births (81.5%, *n* = 22). Overall TOPFA rate for skeletal defects was 37.8% (*n* = 17), but when looking at lethal skeletal dysplasia only, this goes up to 72.2% (*n* = 13).

The shortest median time interval between diagnosis and TOPFA was for CNS anomalies, in particular for anencephaly (7 days), holoprosencephaly (9 days), encephalocele and spina bifida (10 days). The longest time interval between diagnosis and TOPFA was for abdominal wall defects (20.5 days for omphalocele and 22.0 days for gastroschisis), followed by cardiac and skeletal defects. Median time between diagnosis and TOPFA was 12 days (7.0–22.0) for the group with anomalies diagnosed between 11–14 weeks and 11 days (7.7–19.0) for the group with diagnosis between 14 and 21 weeks.

3.1 | Subgroup analysis

Figure 1 presents pregnancy outcome in prenatally diagnosed cases according to the timing of diagnosis of congenital anomalies by

TABLE 3 Structural anomalies by group and timing of diagnosis

Anomalies	Prenatal				Postpartum *n* (%)	Total *n* (%)
	Total	<14 weeks *n* (%)	14–22 weeks *n* (%)	>22 weeks *n* (%)		
CNS anomalies						
Anencephaly	62 (100)	34 (54.8)	28 (45.2)	–	–	62 (12.9)
Encephalocele	12 (92.3)	1 (8.3)	11 (91.7)	–	1 (7.7)	13 (2.7)
Spina bifida	63 (94.0)	3 (4.8)	57 (90.5)	3 (4.8)	4 (6.0)	67 (14.0)
Holoprosencephaly	20 (100.0)	4 (20.0)	14 (70.0)	2 (10.0)	–	20 (4.2)
	157 (96.9)	**42 (26.7)**	**110 (70.1)**	**5 (3.2)**	**5 (3.1)**	**162 (33.9)**
Congenital heart defects						
Tricuspid atresia	14 (100.0)	4 (28.6)	10 (71.4)	–	–	14 (2.9)
Pulmonary atresia	28 (96.6)	1 (3.6)	25 (89.3)	2 (7.1)	1 (3.4)	29 (6.1)
HLHS	49 (94.2)	3 (6.1)	44 (89.8)	2 (4.1)	3 (5.8)	52 (10.9)
	91 (95.8)	**8 (8.8)**	**79 (86.8)**	**4 (4.4)**	**4 (4.2)**	**95 (19.9)**
Skeletal anomalies						
LRD	20 (74.1)	1 (5.0)	19 (95.0)	–	7 (25.9)	27 (5.6)
Lethal skeletal dysplasia[a]	16 (88.9)	2 (12.5)	13 (81.3)	1 (6.3)	2 (11.1)	18 (3.8)
	36 (80.0)	**3 (8.3)**	**32 (88.9)**	**1 (2.8)**	**9 (20.0)**	**45 (9.4)**
Abdominal wall defects						
Gastroschisis	34 (100.0)	12 (35.3)	20 (58.8)	2 (5.9)	–	34 (7.1)
Omphalocele	46 (90.2)	32 (69.6)	13 (28.3)	1 (2.2)	5 (9.8)	51 (10.7)
LBWC, Pentalogy of Cantrell	19 (100.0)	9 (47.4)	10 (52.6)	–	–	19 (4.0)
	99 (95.2)	**53 (53.5)**	**43 (43.4)**	**3 (3.0)**	**5 (4.8)**	**104 (21.8)**
CAKUT						
Megacystis (LUTO)	10 (100)	7 (70.0)	3 (30.0)	–	–	**10 (2.1)**
MCA	61 (98.4)	28 (45.9)	31 (50.8)	2 (3.3)	1 (1.6)	**62 (13.0)**
Total	**454 (95.0)**	**141 (31.0)**	**298 (65.6)**	**15 (3.3)**	**24 (5.0)**	**478**

[a]Including the diagnosis of osteogenesis imperfecta type II, thanatophoric dysplasia and achondrogenesis type I.

ultrasound. In the group of anomalies with diagnosis between 11 and 14 weeks TOPFA was chosen in the majority of cases (75.9%, $n = 107$), spontaneous death occurred in 17.7% ($n = 25$) and live birth in only 6.4% ($n = 9$). In the group with diagnosis between 14 and 22 weeks, TOPFA was chosen in 64% of cases ($n = 191$), spontaneous death occurred in 13.1% ($n = 39$) and live birth in 22.8% ($n = 68$). The rate of TOPFA was higher in the group with diagnosis at 11–14 weeks of gestation compared with the group with diagnosis between 14 and 22 weeks RR 1.18 (95% CI 1.04, 1.34). Figure E1 shows the proportion of TOPFA in pregnancies that had undergone genetic testing (66.4%, $n = 253$) compared to those who did not (48.5%, $n = 47$) RR 1.37 (95% CI 1.10, 1.70). In cases that underwent invasive testing and prenatal genetic diagnosis, TOPFA was more often chosen when the result of genetic testing was abnormal (80.9%, $n = 85$) compared to when this was normal (70.3%, $n = 194$), RR 1.15 (95% CI 1.02, 2.29). (Figure E2).

3.2 | Comment

3.2.1 | Principal findings

The current study investigated the time of diagnosis and pregnancy outcome of a selected group of major structural anomalies with a potential first-trimester detection rate of at least 50%. The main findings are that virtually all anomalies were diagnosed prenatally (95%) and that detection rates and pregnancy outcome varied greatly among the isolated malformations. Most diagnoses (66%) were made in the second trimester of pregnancy (between 14 and 22 weeks of gestation), with a small proportion being detected (3%) after 22 weeks. Notably, in almost 1/3 of cases (31%) the diagnosis was made before 14 weeks of gestation. Pregnancy outcome showed a clear predominance of TOPFA in 63% of pregnancies.

TABLE 4 Genetic anomalies in foetuses with prenatally diagnosed congenital anomalies

Anomalies	Prenatally diagnosed *n*	Genetic test performed *n* (%)		Genetic test result		
				Normal *n* (%)	Abnormal *n* (%)	Abnormal karyotype *n*/all abnormal results *n*, (%)
CNS						
Anencephaly	62	38	(61.3)	32 (84.0)	6 (16.0)	1/6 (16.7%) Triploidy (*n* = 1)
Encephalocele	12	9	(75.0)	7 (77.8)	2 (22.2)	2/2 (100.0) Trisomy 13 (*n* = 2)
Spina bifida	63	42	(66.7)	35 (83.3)	7 (16.7)	5/7 (71.4) Trisomy 18 (*n* = 3) Triploidy (*n* = 1) 48, XXYY (*n* = 1)
Holoprosencephaly	20	20	(100.0)	8 (40.0)	12 (60.0)	11/12 (91.7) Trisomy 13 (*n* = 7) Trisomy 18 (*n* = 1) Triploidy (*n* = 3)
	157	**109**	**(69.4)**	**82 (52.2)**	**27 (47.8)**	
Cardiac						
Tricuspid atresia	14	13	(92.9)	12 (92.3)	1 (7.7)	1/1 (100.0) Trisomy 18 (*n* = 1)
Pulmonary atresia	28	28	(100.0)	24 (85.7)	4 (14.3)	–
HLHS	49	45	(89.9)	42 (85.7)	7 (14.3)	2/7 (28.6) Trisomy 18 (*n* = 1) Monosomy X (*n* = 1)
	91	**86**	**(94.5)**	**74 (86.0)**	**12 (14.0)**	
Skeletal						
LRD	20	12	(60.0)	11 (91.7)	1 (8.3)	1/1 (100.0) Trisomy 18 (*n* = 1)
Lethal skeletal dysplasia	16	16	(100.0)	1 (6.3)	15 (93.8)	–
	36	**28**	**(77.8)**	**12 (42.9)**	**16 (57.1)**	
Abdominal wall						
Gastroschisis	34	20	(58.8)	17 (85.0)	3 (15.0)	3/3 (100.0) Trisomy 18[a] (*n* = 3)
Omphalocele	46	46	(100.0)	18 (39.1)	28 (60.9)	22/28 (78.6) Trisomy 13 (*n* = 1) Trisomy 18 (*n* = 19) Trisomy 21 (*n* = 1) Monosomy X (*n* = 1)
LBWC, pentalogy of cantrell	19	17	(89.5)	15 (88.2)	2 (11.8)	1/2 (50.0) Trisomy 18 (*n* = 1)
	99	**83**	**(83.8)**	**50 (60.2)**	**33 (39.8)**	
Renal						
Megacystis	10	9	(90.0)	4 (44.4)	5 (55.6)	4/5 (80.0) Trisomy 18 (*n* = 4)
MCA	**61**	**50**	**(82.0)**	**42 (84.0)**	**8 (16.0)**	6/8 (75.0) Trisomy 18 (*n* = 5) Trisomy 13 (*n* = 1)
Total	**454**	**365**	**(80.4)**	**264 (72.3)**	**101 (27.7)**	

[a]Possibly cases of ruptured exomphalos prenatally classified as gastroschisis based on ultrasound findings.

TABLE 5 Pregnancy outcome of study population

Anomalies	Pregnancy outcome							
	TOPFA *n* (%)	Diagnosis to TOPFA (*n*. days range)[a]	*N*[b]	Spontaneous death			Live birth *n* (%)	Total *n* (%)
				Foetal *n* (%)	At delivery[c] *n* (%)	Neonatal *n* (%)		
CNS								
Anencephaly	56 (90.3)	7 (3.0,10.3)	34	2 (3.2)	4 (6.4)	–	–	62
Encephalocele	7 (53.8)	10 (5.0, 12.0)	3	1 (7.7)	1 (7.7)	–	4 (30.8)	13
Spina bifida	50 (74.6)	10.5 (8.0, 14.0)	40	–	1 (1.5)	–	16 (23.9)	67
Holoprosencephaly	15 (75.0)	9 (6.0, 12.5)	13	1 (5.0)	4 (20.0)	–	–	20
	128 (79.0)			**4 (2.5)**	**10 (6.2)**	**–**	**20 (12.3)**	**162**
Cardiac								
Tricuspid atresia	9 (64.3)	20 (10.0, 31.8)	6	1 (7.1)	–	–	4 (28.6)	14
Pulmonary atresia	11 (37.9)	16 (14.0, 19.0)	11	1 (3.4)	9 (31.0)	–	8 (27.6)	29
HLHS	34 (65.4)	16 (11.5, 22.0)	25	1 (1.9)	10 (19.2)	–	7 (13.5)	52
	54 (56.8)			**3 (3.2)**	**19 (20.0)**	**–**	**19 (20.0)**	**95**
Skeletal								
LRD	4 (14.8)	14 (8.5, 23.5)	4	1 (3.7)	–	–	22 (81.5)	27
Lethal skeletal dysplasia	13 (72.2)	17 (13.0, 19.0)	8	–	1 (5.6)	4 (22.2)	–	18
	17 (37.8)			**1 (2.2)**	**1 (2.2)**	**4 (8.8)**	**22 (48.9)**	**45**
Abdominal wall								
Gastroschisis	7 (20.6)	22 (11.0, 31.0)	7	1 (2.9)	2 (5.9)	1 (2.9)	23 (67.6)	34
Omphalocele	29 (56.9)	20.5 (9.7, 28.0)	14	3 (5.9)	5 (9.8)	–	14 (27.4)	51
LBWC, pentalogy of Cantrell	16 (84.2)	11 (6.5, 20.0)	3	2 (10.5)	–	1 (5.3)	–	19
	52 (50.0)			**6 (5.8)**	**7 (6.7)**	**2 (1.9)**	**37 (35.6)**	**104**
Renal								
Megacystis	**8 (80.0)**	12 (5.0, 30.0)	7	1 (10.0)	–	1 (10.0)	**–**	**10**
MCA	**41 (66.1)**	16 (8.8, 26.5)	28	14 (22.6)	–	3 (4.8)	4 (6.4)	**62**
Total	**300 (62.8)**		188	**29 (6.1)**	**37 (7.7)**	**10 (2.1)**	**102 (21.3)**	**478**

[a]Period between the diagnosis of the anomaly and the day of TOPFA. Expressed in days as median (IQR range).

[b]Indicates the number of cases with available data on days between diagnosis of the anomaly and TOPFA.

[c]This includes death within the first 24 hours of life.

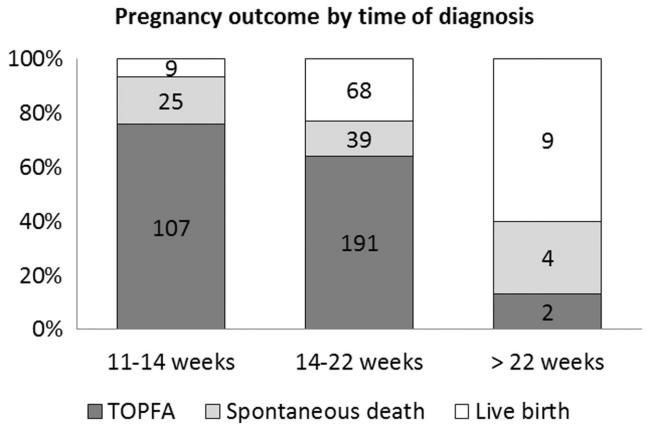

FIGURE 1 Pregnancy outcome by the time of diagnosis

3.2.2 | Strengths of the study

A strength of the study is the use of a population-based cohort from the EUROCAT-NNL dataset, covering all deliveries in the three Northern provinces of the Netherlands. Additionally, EUROCAT works by active case ascertainment, uses internationally recognised disease codification systems and is subject to quality control, therefore increasing comparability and data quality. Second, the complete follow-up with pregnancy outcome also represents a strength of this cohort. Finally, the inclusion of cases with all pregnancy outcomes, including foetal loss and TOPFA, reduces the likelihood of selection bias in our population. This is especially true as the foetuses we studied were affected by congenital anomalies with high mortality rates.[20,21]

3.2.3 | Limitations of the data

The study also has some limitations. First, it should be noted that the national prenatal screening programme was subject to significant changes during the study period. Although these changes only involved the screening for chromosomal anomalies, our findings might have been influenced as well. We were not able to investigate the potential effects of the changes in the prenatal screening programme, because the size of our cohort was too small.

3.2.4 | Interpretation

The finding that detection rates can vary considerably among different anomalies has been previous described.[4,5,22] However, the common denominator of the major structural malformations in our cohort was their potential detectability in the first trimester in at least half of cases.[15] This was achieved in only 3/14 anomalies in the absence of FTAS; anencephaly (54%), omphalocele (70%) and megacystis (70%). Although these anomalies involve different organs and have dissimilar prognoses, all three should always be identified in the first trimester provided that a protocolled FTAS is offered.[5,15] During the study, FTAS was not yet part of the prenatal screening programme, and it is therefore not surprising that these obvious anomalies were most frequently detected during STAS. At the same time, the uptake of the CT was low at about 30%, which also contributes to the low detection rates in the first trimester.[23] In our cohort, women with baseline risk of congenital anomalies who undertook screening in the first trimester only received a quick and unofficial anatomical survey at the time of the nuchal scan, when they opted for the CT. This was usually done while waiting for adequate foetal position for correct NT measurement. During the NT scans about 30% of severe structural defects can be detected.[17]

Timely diagnosis in the first trimester, which frequently reflects the high severity of the anomaly, led to a higher rate of TOPFA, compared to when the diagnosis was made at 14–22 weeks. This underscores the importance of early diagnosis for parents when considering to terminate the pregnancy. In the Netherlands, TOPFA is legally permitted until 24 weeks of gestation.[3] Only in case of lethal anomalies this can be performed at a later gestational age. A recent European study investigating variations in congenital anomaly-related perinatal mortality attributable to TOPFA and prenatal diagnosis has shown that higher prenatal diagnosis rates are associated with higher TOPFA.[6] Although our cohort only included a selected group of foetuses, we confirm this finding. The fact that 92% of anomalies were diagnosed before 22 weeks of gestation allowed parents to choose for TOPFA before the legal limit was reached. Notably, with the exception of QF-PCR which can be analysed in the lab 1–3 working days, genetic investigations by Array-CGH and whole exome sequencing (WES) require about 2–3 weeks before a valid result is provided. Our findings show that pregnancies with an underlying genetic condition are more often terminated compared to those with normal results of genetic testing. This emphasises the importance of early prenatal diagnosis by ultrasound to give parents enough time for an informed decision on the course of pregnancy once the results of genetic testing are accessible. This is especially relevant nowadays, given the advances in laboratory technology and understanding of genetic pathologies in malformed foetuses.[24,25]

Even though all anomalies had a reported first-trimester detection rate of at least 50%, some like anencephaly, holoprosencephaly, abdominal wall defects and megacystis can be diagnosed before 14 weeks in 100% of cases, in contrast to more subtle defects such as spina bifida, LRD and lethal skeletal dysplasia, whose detection rates fluctuate between 50 and 100%.[15,16] It was therefore reassuring to see that all cases of anencephaly and holoprosencephaly were diagnosed prenatally, although a significant number were detected in the second trimester. These brain anomalies are very severe and have an extremely poor prognosis.[26] Both should always be identified by first and second-trimester anatomical screening by visualisation absence of brain tissue or, in case of holoprosencephaly, of the midline.[5,27,28] As expected, none of the foetuses affected by these severe defects was born alive and time between diagnosis and TOPFA was the shortest reported in our cohort (7–9 days).

Another common anomaly affecting the neural tube is spina bifida. In our cohort, 91% of cases were diagnosed in the second

trimester, but an additional 6% ($n = 4$) were only identified postpartum (2 cases of small closed sacral defects and 2 missed by ultrasound). Although first-trimester detection can be achieved, STAS remains the gold standard for prenatal identification of this defect.[29] Spina bifida knows different degrees of severity, mostly depending on the level of the defect and the prognosis is also heterogeneous, as confirmed by our results.[26]

Although we only considered a small proportion of severe cardiac defects, which are amenable to first-trimester diagnosis, it was encouraging to see that almost all were diagnosed prenatally (96%). However, only a minority of cases (9%) were detected in the first trimester, which is not surprising giving the fact that no FTAS was offered. Indeed, compared with the other anomalies included in our cohort, cardiac defects are more subtle and only identifiable by the trained eye when scanning the heart in a systematic way and by use of Doppler flow.[30–32] This goes beyond the scopes of the NT scan but is successfully implemented during STAS.[33]

Abdominal wall defects are also easily identifiable on ultrasound and more than half (54%) were detected before 14 weeks of gestation. Prenatal identification is essential for the organisation of postnatal surgical care. Although omphalocele is more frequently associated with other (structural/genetic) anomalies compared with gastroschisis, when isolated and depending on the size of the herniation both defects can be corrected by postnatal reparative surgery.[27,34,35]

As to urological anomalies, we only considered foetal megacystis, which was diagnosed in 70% of cases before 14 weeks of gestation. Megacystis can have different aetiologies, ranging from lethal to spontaneous resolution in-utero or after birth.[36,37] Notably, in our cohort, only pathological cases were registered in the EUROCAT-NNL data set. Irrespective of the cause, it has been described as an easily detectable anomaly by ultrasound.[5,16,17,27] Although the number of cases was low, it was associated with genetic pathology in more than half of the cases and resulted in TOPFA in 80% of pregnancies.

In our cohort, 26% of LRD were only detected after birth. Although this finding is in line with previous reports, it was somewhat surprising as STAS includes clear guidelines for the correct visualisation of all long bones, as well as the hands and feet.[8,38] A recent study with data from EUROCAT-NNL on prenatal diagnosis of LRD showed that genetic anomalies are more frequent when LRD are paired with MCA and affect more than one limb.[39] Indeed, the vast majority (92%) of isolated LRD that underwent genetic testing in our cohort were normal and with a good outcome. On the contrary, cases with lethal skeletal dysplasia, diagnosed prenatally in 89% of cases, had a poor outcome (TOPFA in 72%) and an underlying genetic aetiology was found in 94% of the prenatally diagnosed cases. Recently, the potentials of WES and advanced skeletal scanning as diagnostic tools for skeletal dysplasia have been stressed.[40,41] However, especially in the first years of study inclusion WES was not yet consistently offered in our cohort.

4 | CONCLUSIONS

Major structural anomalies amenable to early diagnosis in the first trimester of pregnancy are mostly diagnosed during the second trimester in the absence of a regulated first-trimester anatomical screening programme. Detection rates and pregnancy outcome show evident variation among the different types of malformations with higher early detection rates for more lethal and evident malformations. Pregnancy outcome is poor in these foetuses and especially in cases with first-trimester diagnosis and abnormal genetic testing.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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