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ORIGINAL RESEARCH ARTICLE

Prenatal detection of major congenital malformations in a cohort of 19 367 Danish fetuses with a complete follow-up six months after birth

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Abstract

Introduction: To investigate the performance of the second-trimester ultrasound scan regarding ultrasound-detectable congenital malformations in a Danish region. The study sample was population-based, with 6 months of postnatal follow-up. Hospital records and autopsy reports were reviewed in each case to validate the prenatal ultrasound diagnosis.

Material and methods: This population-based cohort study included all fetuses ($n = 19.367$) alive at the second-trimester scan in four hospitals in a Danish region. The final diagnosis of the malformations was based on hospital records during the 6-month postnatal follow-up. In case of termination or stillbirth, the result from the autopsy report was used to validate the prenatal ultrasound diagnosis.

Results: The detection rate of congenital malformations in the prenatal screening program was 69%, where 18% was detected on the first-trimester scan and 51% on the second-trimester scan. Another 8% was detected in the third trimester. Specificity was 99.9%. The positive predictive value of the screening program was 94.5%, and the negative predictive value was 99.5%. The overall prevalence of malformations was 16.8 per 1000 fetuses, most frequently in the heart and the urinary tract.

Conclusions: This study shows that the national screening program for congenital malformations can detect many severe malformations and is an effective screening test for malformations.

KEYWORDS
congenital malformation, genetic disorder, genetic testing, prenatal detection, prenatal screening, ultrasound

1 | INTRODUCTION

Since 2004, all pregnant women in Denmark have been offered a combined first-trimester screening and a second-trimester scan by the Danish Health Authority.[1] The nationally implemented prenatal screening was considered especially important in cases where (1) immediate postnatal treatment in a highly specialized hospital is essential to reduce mortality and morbidity, (2) the malformation may be a marker for genetic disorders, and (3) termination of pregnancy is an option.[1] Attendance at the screening program was approximately 94%.[2]

A Danish study from 2016 showed high performance of the combined first-trimester screening at a national level (5). A national fetal medicine database (The Danish Fetal Medicine database) was established to assess the prenatal screening program.[3] However, it was not possible to evaluate the performance of the second-trimester scan due to inconsistent registration of malformation diagnoses.[3] Audit of a few selected diagnoses in the Danish Fetal Medicine database showed a considerable difference between these data and the audited hospital records.

The objective of this study was to investigate the performance of prenatal scans regarding ultrasound-detectable congenital malformations in a Danish region. The study sample was population-based, with 6 months of postnatal follow-up. Hospital records and autopsy reports were reviewed in each case to validate the prenatal ultrasound diagnosis.

2 | MATERIAL AND METHODS

This study was conducted as a population-based cohort study with prospectively collected data between February 2014 and September 2016, including all fetuses (n = 19.477 consisting of singletons [n = 19.075], twins [n = 192] and triplets [n = 6]) in the first-trimester scan (FTS) and the second-trimester scan in the four hospitals in the Region of Southern Denmark. The hospitals included one tertiary center and three community hospitals. Pregnant women from the community hospitals were referred to the tertiary center if a second opinion or multidisciplinary counseling of the parents was needed.

The ultrasound examinations in the prenatal screening program were offered to all pregnant women free of charge and were mainly performed transabdominal. Sonographers performed the scans in accordance with the national guidelines of the Danish Fetal Medicine Society. Sonographers and doctors were certified in performing the first- and second-trimester scans in accordance with the Fetal Medicine Foundation. The FTS was performed between gestational weeks 11 + 3 and 13 + 6 and included an ultrasound examination to verify the fetus's viability, determine gestational age, the number of fetuses, and the overall fetal anatomy. In addition, the women could opt for a risk assessment for trisomy 13, 18, and 21. Invasive genetic testing (chorionic villus sampling or amniocentesis) was offered in case of a high-risk assessment (trisomy 21 1:300, trisomy 13 and 18 1:150) or selected cases with ultrasound-detected malformations.
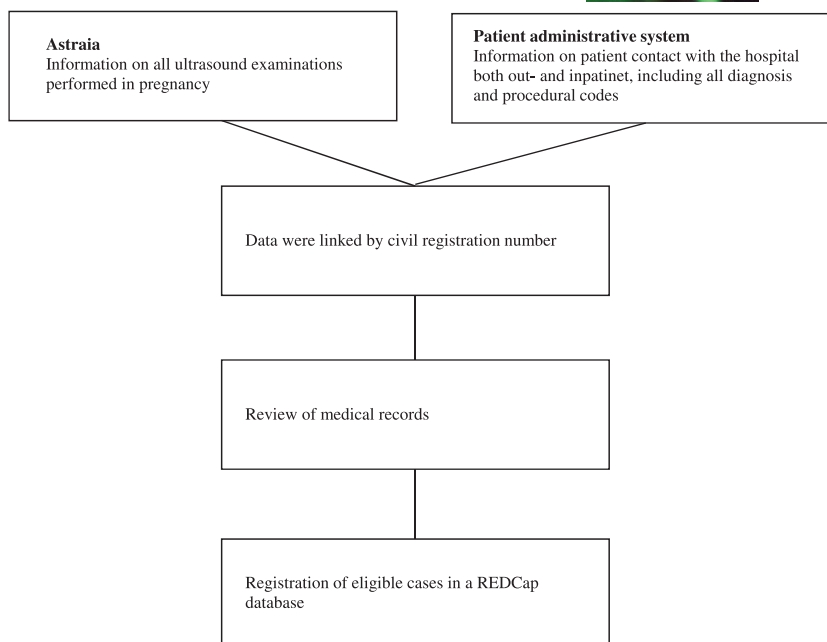
> **Key message**
>
> Ultrasound scanning is a good screening test for congenital malformations and can detect many severe malformations with few false-positive cases. The screening program had high positive predictive (94.5%) and negative predictive values (99.5%).

The samples were analyzed using microarray. The second-trimester scan was carried out between gestational weeks 19 and 21–22 using a standardized protocol, including the cardiac outflow tract. Ultrasound examinations in the third trimester were performed on obstetric indications (eg fetal growth restriction) and are not part of the prenatal screening program. After birth, midwives examined all infants. If the examination was abnormal, the infant was referred to a pediatrician or other specialists for further examination. In cases with prenatal detection of severe malformations and poor prognosis, the parents could apply for termination of pregnancy due to fetal abnormality (TOPFA).

We used patient administrative systems and the ultrasound database Astraia (Astraia software gmbh, version 1.24.7, Germany, https://www.astraia.com/en/) to identify the study population, including live births, spontaneous abortions, terminated pregnancies due to fetal malformation, and stillbirths. Each hospital provided data on the study population (discharge codes and outpatient contacts) using codes from ICD-10 (International Statistical Classification of Diseases and Related Health Problems). Data for the study included diagnosis for both in- and outpatients at the obstetric and pediatric departments with a follow-up period of 6 months after delivery. All obstetric departments in Denmark use Astraia. We used Astraia to identify the study population of fetuses attending the FTS and second-trimester scan using procedural codes UXUD86A, UXUD86B, ICD-10 codes DQ 00–99, and detailed information about malformations. Patient administrative systems provided data from the obstetric departments on TOPFA and intrauterine death due to an abnormality (DO053, DO054, DO058, DO059, DO364, and DO359A). Data on infants with congenital malformations (DQ00–99) were obtained from the patient administrative system in the pediatric departments. Data from the patient administrative systems are directly reported to the Danish National Patient Registry and are not transformed. Data are considered to have the same validity across hospitals.[4] We used data from the patient administrative systems instead of data from the Danish National Patient Registry due to a delay in the transfer of data from the patient administrative system to the Danish National Patient Registry.

Data on the mother and infant were linked using the unique civil registration number given to all Danish citizens at birth (Figure 1). Persons without a permanent civil registration number (eg refugees and immigrants) were given a temporary civil registration number at their first contact with Danish healthcare. The civil registration numbers were used to identify unique cases and for identification in

FIGURE 1 Data sources for the study.

Astraia
Information on all ultrasound examinations performed in pregnancy

Patient administrative system
Information on patient contact with the hospital both out- and inpatinet, including all diagnosis and procedural codes

Data were linked by civil registration number

Review of medical records

Registration of eligible cases in a REDCap database

the medical records, data validation, and to ensure that no duplicates were included in the final cohort.

We used hospital records and Astraia to validate all cases and to determine if the malformation was detected pre- or postnatal. A malformation was classified as prenatally detected if the prenatal diagnosis was in the same organ system as the postnatal diagnosis. Hospital records, including genetic reports, were used to determine if there was an additional genetic disorder and if the genetic diagnosis was made before or after the malformation diagnosis. The final diagnosis of the infants was postnatal diagnoses based on hospital records and, if relevant, autopsy reports in the six-month follow-up period. Results from the last ultrasound examination were used as a diagnosis in cases of intrauterine death, stillbirth, and TOPFA if an autopsy was not performed.

We excluded fetuses with a malformation where the mother did not attend any ultrasound examinations, moved out of the region during pregnancy, or attended the prenatal screening program outside the Region of Southern Denmark or in a private setting. Pregnant women from other regions in Denmark referred to the tertiary center for specialized function in pediatric surgery were also excluded.

Fetuses with a large nuchal fold or a high risk of trisomy 13, 18, and 21 were classified as abnormal if the invasive test showed a genetic disorder and were excluded from this study. The fetus was classified as normal if the genetic result was normal and the infant was healthy after birth. Fetuses with postnatal diagnosed trisomy 21, low risk of the FTS, a normal second-trimester scan, and no postnatal diagnosed malformations were excluded from the study.

2.1 | Outcome measures

We included all malformations considered detectable by prenatal ultrasound and classified the malformations in line with the European Surveillance of Congenital Anomalies (EUROCAT) definition.[5] Minor malformations and malformations undetectable by ultrasound, such as hypospadias and small muscular ventricular septal defects, were excluded. Excluded malformations are listed in Table S1.

We defined isolated malformation as one or more malformations in the same organ system and multiple malformations as major malformations in two or more organ systems. If a malformation was detected before a genetic disorder, the case was classified as an isolated malformation according to the organ system and not as a genetic disorder. We reviewed the hospital records in each case to determine if the malformation or genetic disorder occurred first. According to the organ system, the prenatal detection rate (DR) was calculated for each of the included malformations. Unspecific ultrasound findings, such as small biometrics, were classified as syndromes if genetic testing showed a pathogenic genetic disorder.

Major other fetal diseases were fetal diseases that are lethal or associated with severe morbidity unrelated to malformations. Prenatal malformations were defined as minor if they were associated with minor or no long-term morbidity and were not included in the category of organ systems.

We classified malformations as false-positive if a prenatally suspected malformation was not confirmed in the six-month follow-up period after birth. Malformations suspected in the prenatal screening program but refuted by a scan later in pregnancy were classified as normal. These infants were not scheduled for postnatal follow-up by a pediatrician.

Ventriculomegaly was considered present if the atrial width was ≥10 mm at the second-trimester scan. Hydronephrosis was defined as pelvicalyceal dilatation with an anteroposterior diameter ≥ 5 mm at the second-trimester scan.

We classified congenital heart defects (CHD) according to Watkins et al.[6] (1) Critical CHD (intervention in the newborn period or early infancy to ensure the survival of the infant), (2) major CHD

(intervention required in early infancy to ensure optimal long-term outcome), (3) CHD that typically manifests later in infancy (intervention required to prevent long-term sequelae in adulthood) and (4) minor CHD (no intervention is required to ensure long-term and symptom-free survival).[6] We did not have any cases in the category of CHD that manifested later in infancy due to the six-month follow-up period. All fetuses with a confirmed diagnosis of perimembranous ventricular septal defects within the first 6 months after birth were included.

A diagnosis of clubfoot was only considered positive if the infant received surgical or Ponseti treatment.

Infants with postnatally diagnosed clubfoot or cleft palate may be referred directly to the specialist center without contacting the pediatric outpatient clinics. Consequently, there is no information about these conditions in the pediatric hospital records. We did not obtain supplementary data from these departments.

Infants without a diagnosis of a congenital malformation in the patient administrative systems within the region and within the first 6 months after the birth were assumed not to have malformations and were categorized as normal infants.

Data regarding eligible malformation cases were collected, managed, and stored using research electronic data capture (REDCap) hosted at open patient data explorative network (OPEN), Odense University Hospital, Region of Southern Denmark. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

2.2 | Statistical analyses

Prevalence, sensitivity, specificity, positive predictive value, negative predictive value, false-negative rate, false-positive rate, and false-omission rate were calculated using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Descriptive data are presented as numbers and percentages.

2.3 | Ethics Statement

All analyses were carried out in accordance with Danish guidelines and regulations. The study was approved by the Danish Data Protection Agency (May 2, 2014; 18/43849). Access to register-based health data and data from medical records was granted by the Danish Health Authority (May 19, 2015; 3-3013-806/1/). The Ethics Committee of Health Research Ethics for Southern Denmark (May 19, 2014; S-20142000HLP) waived the need for informed consent.

3 | RESULTS

The study population (n = 19.367) is shown in Figure 2.

The prevalence and overall prenatal DR of malformations stratified on the organ system (isolated or not isolated) are shown in Table 1. The prevalence of malformations and severe fetal disease was 16.8 per 1000 fetuses (Table 1).

In the screening program (FTS and second-trimester scan), the overall prenatal DR was 69% (225/328), where 18% (59/328) was detected at the FTS and 51% (166/328) at the second-trimester scan
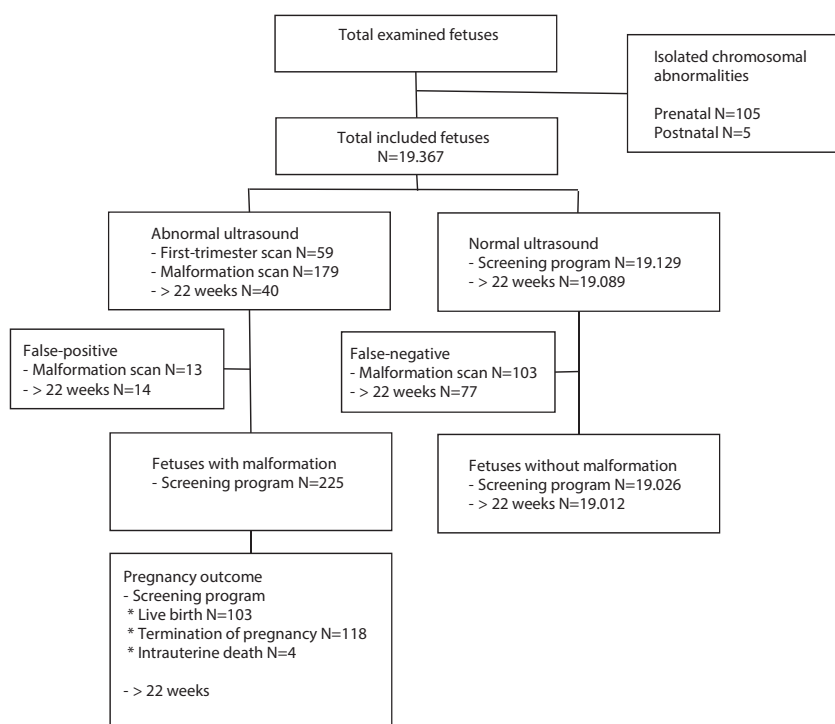

FIGURE 2 The study population of fetuses attending ultrasound screening for congenital malformations.

TABLE 1 Prevalence and detection rate of isolated/nonisolated malformations according to organ system.

| Defect | Total | Prenatal | | | | | | Postnatal | | Prevalence |
		First-trimester scan		Second-trimester scan		>22 weeks				
Isolated malformation	284	43	(15.1)	143	(50.4)	23	(8.1)	75	(26.4)	14.7
Neural tube defect	19	4	(21.1)	13	(68.4)	0	(0.0)	2	(10.5)	1.0
Other central nervous systems	36	15	(41.7)	11	(30.6)	5	(13.9)	5	(13.9)	1.8
Facial cleft	17	0	(0.0)	13	(76.5)	1	(5.9)	3	(17.7)	0.9
Thorax	10	2	(20.0)	6	(60.0)	0	(0.0)	2	(20.0)	0.5
Congenital heart defects	79	0	(0.0)	34	(43.0)	2	(2.5)	43	(54.4)	4.1
Urinary tract	69	4	(5.8)	48	(69.6)	10	(14.5)	7	(10.1)	3.6
Abdominal wall defect	16	15	(93.6)	0	(0.0)	1	(6.3)	0	(0.0)	0.8
Digestive system	13	1	(7.7)	1	(7.7)	3	(23.1)	8	(61.5)	0.7
Musculoskeletal system	23	2	(8.7)	15	(65.2)	1	(4.3)	5	(21.7)	1.2
Tumor	2	0	(0.0)	2	(100.0)	0	(0.0)	0	(0.0)	0.1
Multiple malformations	28	8	(28.6)	18	(64.3)	0	(0.0)	2	(7.1)	1.4
Syndrome	1	0	(0.0)	1	(100.0)	0	(0.0)	0	(0.0)	0.1
Major other fetal diseases	12	8	(66.7)	3	(25.0)	1	(8.3)	0	(0.0)	0.6
Minor malformation	3	0	(0.0)	1	(33.3)	2	(66.7)	0	(0.0)	0.2
Total	328	59	(17.9)	166	(50.6)	26	(7.9)	77	(23.5)	16.8

Note: Data are given as *n*, *n* (%), or per 1000 fetuses.

(Table 1). The overall prenatal DR increased to 77% if malformations detected in the third trimester were included.

All cases of anencephaly, diaphragmatic hernia, megacystis/urethral valves, omphalocele, and most cases of cleft lip, abdominal wall defects, clubfoot, and multiple malformations were detected. Malformations with detection <50% included agenesis of the corpus callosum, bowel atresia, and anal/rectal atresia (Table 2).

The FTS detected all megacystis/urethral valves and omphalocele cases, 92% of cases of anencephaly, 89% of gastroschisis, and 92% of other major fetal diseases. Detection in the third trimester was mainly malformations in the central nervous system, gastrointestinal tract, and hydronephrosis (Table 2).

The most common malformation was CHD, with a prevalence of 4.1 per 1000 fetuses and an overall prenatal DR of 43% (34/79) in the screening program (Table 1). However, prenatal DR for critical CHD was 67% (22/33), and DR for major CHD was 57% (4/7) in the screening program (Table 2). All cases of hypoplastic left heart syndrome and tetralogy of Fallot were diagnosed in the screening program. There were 43 false-negative cases; five (12%) were critical CHD cases that required operation shortly after birth. None of the remaining false-negative CHD cases underwent an operation in the six-month follow-up after birth. Two false-positive cases were suspected of minor CHD (Table 2).

The second most common group of malformations was in the urinary tract system, with a prevalence of 3.6 per 1000 (Table 1). The prenatal DR was overall 75% in the screening program and included most of the severe malformations. There were seven (10%) false-negative cases, of whom two were diagnosed postnatally with severe renal malformation and five with minor malformations (Table 2).

Malformations in the central nervous system were the third most common group, with a prevalence of 2.8 per 1000 and an overall

prenatal DR of 78% in the screening program (Table 1). All cases of anencephaly were detected. Over 80% of spina bifida, hydrocephalus, and holoprosencephaly cases were detected in the screening program. Five central nervous system cases were detected after week 22. There were seven (13%) false-negative central nervous system cases, where four were diagnosed with severe malformation and three with a minor (Table 2). There were three false-positive cases. All were suspected of minor malformations (Figure 1).

The prenatal DR of multiple malformations in the screening program was 93% and a prevalence of 1.4 per 1000 (Table 1). There were two (7%) false-negative cases where one required an operation after birth (Table 2).

The prenatal DR of musculoskeletal malformations in the screening program was 74%, with a prevalence of 1.2 per 1000 (Table 1). Most cases of clubfoot (80%) and skeletal dysplasia (75%) were detected in the screening program. There were five (22%) false-negative cases that all required treatment. Three false-positive cases consisted of suspected clubfoot.

The prenatal DR of facial cleft malformations was 77% in the screening program, with a prevalence of 0.9 per 1000 (Table 1). There were three (18%) false-negative cases with cleft lip and palate requiring treatment.

The prenatal DR of abdominal wall defects was 94% in the screening program, with a prevalence of 0.8 per 1000 (Table 1).

The prenatal DR of malformations in the digestive system was 15% in the screening program, with a prevalence of 0.7 per 1000 (Table 1). There were eight (62%) false-negative cases requiring an operation postnatally. There were three false-positive cases, all suspected of bowel atresia.

The prenatal DR of other major fetal diseases was 92% in the screening program, with a prevalence of 0.6 per 1000 (Table 1).

TABLE 2 Prenatal detection rate of malformations according to malformation subgroups.

Defect	Total	Prenatal			Total	Postnatal	Additional genetic disorder	
		First-trimester scan	Second-trimester scan	>22 weeks			Prenatal	Postnatal
Central nervous system								
Anencephaly	13	12 (92.3)	1 (7.7)	0 (0.0)	13 (100.0)	0 (0.0)	0	0
Spina bifida	19	4 (21.1)	13 (68.4)	0 (0.0)	17 (89.5)	2 (10.5)	0	0
Hydrocephalus/ventriculomegaly	5	1 (20.0)	3 (60.0)	0 (0.0)	4 (80.0)	1 (20.0)	0	0
Holoprosencephaly	5	1 (20.0)	3 (60.0)	0 (0.0)	4 (80.0)	1 (20.0)	1	0
Agenesis of the corpus callosum	3	0 (0.0)	1 (33.3)	1 (33.3)	2 (66.7)	1 (33.3)	0	0
Intracerebral cysts	1	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	0	0
Other	9	1 (11.1)	3 (33.3)	3 (33.3)	7 (77.8)	2 (22.2)	2	2
Face								
Facial cleft (cleft lip)	17	0 (0.0)	13 (76.5)	1 (5.9)	14 (82.4)	3 (17.7)	2	0
Thorax								
Diaphragmatic hernia	5	2 (40.0)	3 (60.0)	0 (0.0)	5 (100.0)	0 (0.0)	0	0
Pulmonary adenoid malformation	5	0 (0.0)	3 (60.0)	0 (0.0)	3 (60.0)	2 (40.0)	0	0
Congenital heart defects (CHD)								
Transposition of the great arteries[a]	6	0 (0.0)	2 (33.3)	1 (16.7)	3 (50.0)	3 (50.0)	0	0
Coarctation of aorta[a]	6	0 (0.0)	3 (50.0)	1 (16.7)	4 (66.7)	2 (33.3)	0	0
(Total) anomalous pulmonary venous return[a]	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	0	0
Hypoplastic right heart syndrome[a]	8	0 (0.0)	7 (87.5)	0 (0.0)	7 (87.5)	1 (12.5)	0	0
Hypoplastic left heart syndrome[a]	10	0 (0.0)	10 (100.0)	0 (0.0)	10 (100.0)	0 (0.0)	3	0
Ebsteins anomaly[b]	1	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0	0
Atrioventricular septal defect[b]	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	0	1
Tetralogy of Fallot[b]	2	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	1	0
Common arterial trunk[b]	1	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0	0
Ventricular septal defect[c]	31	0 (0.0)	4 (12.9)	0 (0.0)	4 (12.9)	27 (87.1)	0	3
Valve anomalies[c]	5	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)	4 (80.0)	0	1

TABLE 2 (Continued)

Defect	Total	Prenatal				Postnatal	Additional genetic disorder	
		First-trimester scan	Second-trimester scan	>22 weeks	Total		Prenatal	Postnatal
Right aortic arch and vascular ring[c]	1	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0	0
Persistent left superior vena cava[c]	2	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	0	0
Urinary tract								
Hydronephrosis	42	0 (0.0)	29 (69.0)	9 (21.4)	38 (90.5)	4 (9.5)	0	1
Renal agenesis (uni- and bilateral)	6	0 (0.0)	5 (83.3)	0 (0.0)	5 (83.3)	1 (16.7)	0	0
Autosomal recessive polycystic kidney disease	4	0 (0.0)	2 (50.0)	0 (0.0)	2 (50.0)	2 (50.0)	0	0
Renal dysplasia	10	0 (0.0)	10 (100.0)	0 (0.0)	10 (100.0)	0 (0.0)	0	1
Megacystis/urethral valves	4	4 (100)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0	1
Other	3	0 (0.0)	2 (66.7)	1 (33.3)	3 (100.0)	0 (0.0)	0	0
Abdominal wall defects								
Omphalocele	7	7 (100.0)	0 (0.0)	0 (0.0)	7 (100.0)	0 (0.0)	1	2
Gastroschisis	9	8 (88.9)	0 (0.0)	1 (11.1)	9 (100.0)	0 (0.0)	0	0
Digestive system								
Esophageal atresia	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0	0
Bowel atresia	6	0 (0.0)	1 (16.7)	3 (50.0)	4 (66.7)	2 (33.3)	2	0
Anal/rectal atresia	5	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	4 (80.0)	0	0
Musculoskeletal								
Skeletal dysplasia	4	1 (25.0)	2 (50.0)	0 (0.0)	3 (75.0)	1 (25.0)	1	3
Limb reduction defect	2	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0	0
Clubfoot	15	0 (0.0)	12 (80.0)	1 (6.7)	13 (86.7)	2 (13.3)	1	1
Other	2	0 (0.0)	1 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)	1	0
Syndromes	1	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	1	0
Multiple malformations	28	8 (28.6)	18 (64.3)	0 (0.0)	26 (92.9)	2 (7.1)	3	5
Major other fetal disease	12	8 (66.7)	3 (25.0)	1 (8.3)	12 (100.0)	0 (0.0)	3	0
Minor prenatal malformations	3	0 (0.0)	1 (33.3)	2 (66.7)	3 (100.0)	0 (0.0)	0	0
Tumor	2	0 (0.0)	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	0	1
Total	328	59 (17.9)	166 (50.6)	26 (7.9)	251 (76.5)	77 (23.5)	22	22

Note: Data are given as *n* or *n* (%). Genetic disorders include aneuploidies, sex chromosomal abnormalities, mutations and pathogenic copy number variation, detected pre- or postnatal.

[a]Critical CHD.

[b]Major CHD.

[c]Minor CHD.

Cases consisted of fetal hydrops, hygroma, chylothorax, and hypertrophic cardiomyopathy.

All cases of diaphragmatic hernia were detected in the screening program, and 60% of cases with pulmonary cystic adenoid malformation. Prevalence was 0.5 per 1000. There were two false-negative cases and one false-positive case with pulmonary adenoid malformation.

The prenatal DR of minor malformations consisting of ovarian cysts was 33% in the screening program. Prevalence was 0.2 per 1000, and there were two false-positive cases.

The screening program detected two cases of lymphangioma and immature teratoma tumors. Prevalence was 0.1 per 1000.

Additional genetic disorders ($n=44$, 13%), detected after ultrasound diagnosis of malformations, are shown in Table 2. These include 16 cases with aneuploidy, 17 with pathogenic copy-number variation, two with sex chromosomal abnormality, and nine with monogenic disorders undetectable by microarray. Twenty-five cases were diagnosed prenatally by chorionic villi sample or amniocentesis. An additional genetic disorder was diagnosed in nine cases after the termination of pregnancy and 10 cases after birth.

The false-positive rate in the screening program was 0.1% (13/19039), and the false-negative rate was 31% (103/328) (Figure 1). Six false-negative cases were later diagnosed with an additional genetic disorder (four monogenic disorders, one copy number variation, and one aneuploidy).

The screening program correctly identified 19.026 of 19.039 fetuses with no disease, giving the screening program a specificity of 99.9%. Of the 238 fetuses with a suspected malformation in the screening program, 225 had a confirmed malformation postnatally, giving a positive predictive value of 94.5%. Of the 19.129 fetuses with normal ultrasound examinations in the screening program, 19.026 were confirmed healthy after birth, giving a negative predictive value of 99.5% and a false-omission rate of 0.5%.

4 | DISCUSSION

In our study, the prenatal DR of congenital malformations was 69% in the screening program, 18% were detected on the FTS, and 51% were detected on the second-trimester scan.

Recent studies show it is possible to detect between 27.6% and 43.1% of malformations at the FTS using a standardized anatomic protocol.[7,8] This is higher than our study (17.9%) where a standardized anatomic protocol in the first trimester was not used. This finding may support the hypothesis that using a standardized anatomic protocol on the FTS is crucial in improving the DR on the FTS.

It is difficult to compare results among DR studies due to differences in study settings, classification, and inclusion criteria.[9] Recent studies reported DR from 37% to 81% before gestational week 24.[7,9–11] This may be due to different inclusion criteria of malformations.[10,11] We only included malformations detectable by ultrasound. Improved quality of ultrasound equipment, national guidelines, and education could also contribute to a higher DR.

In our study, the prenatal DR for CHD was low, which is consistent with other studies.[9–11] The low DR (42%) of CHD was mainly due to postnatal diagnosed perimembranous ventricular septal defects, the most frequent CHD (40%). Most of these infants were examined by echocardiography postnatally and not referred for surgery. The etiology of ventricular septal defect (VSD) is not fully understood. Studies suggest that VSD occurs due to a complex interaction of genetic and environmental factors (multifactorial).[12] Ventricular septal defects may be associated with a variety of genetic disorders. The frequency of associated genetic disorders for prenatally diagnosed perimembranous VSD depends on the presence of a first-trimester screening. The risk of associated genetic disorders for fetuses with perimembranous VSD in the second trimester will be lower if fetuses with trisomies are diagnosed and terminated in the first trimester.[13,14] From a clinical perspective, prenatal detection of ventricular septal defects without a genetic disorder is less critical as it is often asymptomatic at birth, and there is no need for immediate treatment. Prenatal detection may lead to increased parental stress during pregnancy.

The prenatal DR of critical CHD was 67%, and the prenatal DR of major CHD was 57% in the screening program. Prenatal detection is essential in the critical and major groups as a large proportion require intensive therapy or surgery shortly after birth to improve survival and reduce neonatal morbidity.[15,16]

Recent Danish studies show that the DR of major CHD increased from 4.5% in 1996 to 71% in 2013 and 89% in 2018.[17,18] However, detection did not increase equally for all CHD. Detection was low for coarctation of the aorta, whereas detection of univentricular hearts had increased considerably.[17] This is consistent with our findings regarding the coarctation of the aorta and the univentricular hearts (Table 2). Improved ultrasound equipment and technical skills, including implementation of outflow-tract and three-vessel views, have increased the detection of most CHDs.[17]

In line with other studies,[9,11] we found a high prenatal DR for malformations in the central nervous system (78%) and urinary tract system (75%). Closed spina bifida can be challenging to detect prenatally because of missing ultrasound signs.[19,20] Malformations such as ventriculomegaly and dysgenesis of the corpus callosum evolve with advancing gestational age and may first become apparent in the third trimester.[21]

The most frequent false positive ultrasound diagnosis in this and other studies was hydronephrosis.[11,22,23] It is well known that hydronephrosis changes over time and, in many cases, resolves in the third trimester.

Our low prenatal DR of malformations in the digestive system is in line with other studies. A common challenge for these malformations is that the prenatal ultrasound signs can be nonspecific and transient.[24,25] Further, these malformations may not be visible at the second-trimester scan and are reported to appear during the late second and third trimesters.[7,21] Overall, there is a low correlation between ultrasound signs and malformations in the digestive system seen after birth.

The false-positive rate was 0.1% in our study and consistent with other studies.[11,26] False-positive rates in prenatal DR studies

are influenced by the included malformations and differences in the definition of false-positive cases. Any suspected malformation may lead to unnecessary parental concern and expensive and unnecessary examinations, including invasive testing and TOPFA.[22] In our study, false-positive diagnoses were mostly malformations with good prognoses. None of the false-positive cases underwent invasive testing or TOPFA but attended more examinations.

The prevalence of major ultrasound-detectable malformations of the screened fetuses was 16.8 per 1000 fetuses. Three studies on prenatal DR with similar designs found a prevalence of malformations ranging between 17.0 and 18.0 per 1000 fetuses.[7,10,11] However, these studies included minor malformations, which we excluded. Other factors that may cause variation in prevalence can be geographical differences due to genetic predisposition or the frequency of risk factors such as consanguinity, pregestational diabetes, maternal obesity, teratogenic drugs, and smoking.[27,28]

The main strength of the study is the unselected low-risk cohort. Participation in the prenatal screening program is high in Denmark.[29] The external validation was high due to confirmation by autopsies and a six-month follow-up, making it possible to stratify CHDs based on surgical intervention.

We were able to validate all cases registered with a malformation diagnosis due to the unique civil registration numbers. Agreement between pre- and postnatal diagnosis in each case was verified using Astraia and the hospital record.

We assume the risk of misclassification of postnatal diagnosis is low because most malformations were diagnosed before the infant's discharge from the maternity unit. However, we may have missed late diagnosed malformations, that is, clubfoot and cleft palate. These malformations may be directly referred to specialist treatment from the health visitor or general practitioner after discharge. We did not obtain data from other than the obstetric and pediatric departments. Another potential limitation is the misclassification of postnatal diagnosis due to inaccurate coding. It was not possible to validate all cases after TOPFA because some parents deselected autopsy.

An autopsy was performed in 50.0% of the cases after TOPFA. In approximately half of the cases where an autopsy was not performed, the malformation was visible at birth or after TOPFA, that is, omphalocele and open spina bifida.

The prenatal screening program detected a high proportion of severe malformations. However, some postnatally detected cases would have benefitted from prenatal detection to ensure an immediate postnatal treatment in a tertiary center. Others would have been offered prenatal genetic testing because the malformation could be a marker for a genetic disorder. In a few cases, termination of pregnancy could potentially have been an option. A prenatal diagnosis would not have changed postnatal examinations, treatment, and prognosis for most postnatal detected malformations.

In the future, improvement of prenatal DR may be possible with the incorporation of a standardized protocol for malformations detectable at the FTS and in the third trimester, look for malformations where the detection is important for the immediate treatment after delivery and/or the long term prognosis (eg coarctation of the aorta, ventriculomegaly) in cases where ultrasound is performed for other indications such as fetal growth restriction.

This study illustrates the need for repeated, systematic audits, especially where prenatal detection is essential for the infant's prognosis. Audit increases focus on malformations with low DRs. Less severe malformations with good prognoses are also important to detect prenatally because they can be markers for pathogenic genetic disorders. Our study found that 20% of cases with valve anomalies, 13% clubfoot, and 10% VSD had an additional pathogenic genetic disorder. This is in line with other studies.[30]

5 | CONCLUSION

This study shows that the national screening program for congenital malformations can detect many severe malformations and is an effective screening test with high positive and negative predictive values and few false-positive cases.

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SUPPORTING INFORMATION

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