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Published in:
Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology

DOI:
10.1002/uog.26249

Publication date:
2023

Document version:
Accepted manuscript

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Prevalence and detection rate of major congenital heart disease in twin pregnancies in Denmark

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Short title: Prevalence and detection of heart disease in twins

Keywords: Congenital heart disease, congenital heart defect, prenatal detection rate, twin pregnancies, prenatal screening, twins

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.26249

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CONTRIBUTION

What are the novel findings of this work?

The prevalence and detection rate of major congenital heart disease (mCHD) in twins without twin-to-twin transfusion syndrome (TTTS) was 4.6 per 1,000 pregnancies. This is the first study to investigate the detection rate (DR) and prevalence of mCHD in both dichorionic and monochorionic twins without TTTS in a larger, non-selected cohort, undergoing a standardized screening and surveillance program.

What are the clinical implications of this work?

The prevalence and prenatal detection of mCHD in twins without TTTS is comparable to singleton pregnancies which is important to include in prenatal counseling. Moreover, it emphasizes the strengths of a national, standardized screening program. Ways to overcome the challenges when screening for CHD in overweight women should be explored further.

ABSTRACT

Objective: To investigate the prevalence and national prenatal detection rate (DR) of major CHD (mCHD) in twin pregnancies without twin-to-twin transfusion syndrome (TTTS)-associated CHD in a population following a universal, standardized prenatal screening program.

Methods: All Danish twin pregnancies are offered standardized screening and surveillance programs besides the 1st and 2nd-trimester screening for aneuploidies and malformation, respectively: Monochorionic twins every two weeks from gestational week 15, and dichorionic twins every four weeks from week 18. The study was performed retrospectively with prospectively collected data. The data were retrieved from the Danish Fetal Medicine Database and included all twin pregnancies from 2009-2018, where at least one fetus had a mCHD diagnosis pre- and/or postnatally. A mCHD was defined as a CHD requiring surgery within the first year of life, excluding ventricular septal defects. All pregnancies were pre- and postnatally validated in the local patient files at the four tertiary centers covering the entire country.

Results: A total of 60 cases from 59 pregnancies were included. The prevalence of mCHD in twins was 4.6 per 1,000 twin pregnancies (95% confidence interval (CI) 3.5-6.0) (1.9 per 1,000 liveborn children (95% CI 1.3-2.5)). The prevalence for DC and MC were 3.6 (95% CI 2.6-5.0) and 9.2 (95% CI 5.8-13.7) per 1,000 pregnancies, respectively. The national DR of mCHD in twin pregnancies for the entire period was 68.3%. The highest detections were in cases with univentricular hearts (100%) and the lowest with a total anomaly of the pulmonary venous return, Ebstein's anomaly, aortic valve stenosis, and coarctation of the aorta (0-25%). Mothers of children with undetected mCHD had a significantly higher BMI compared to mothers of children with a detected mCHD (median 27 and 23, respectively, p=0.03).

Conclusions: The prevalence of mCHD in twins was 4.6 per 1,000 pregnancies, and more frequent in MC twins. Moreover, the DR of mCHD in twin pregnancies was 68.3%. A higher maternal BMI was more frequent in cases of undetected mCHD.

INTRODUCTION

Congenital heart disease (CHD) is a frequent birth defect and is reportedly higher in twins than in singleton pregnancies[1-5]. CHD ranges from mild to severe, where major CHD (mCHD) usually requires surgery within the first year of life and is known to be associated with increased morbidity and mortality in early childhood [6].

The reported prevalence of mCHD in mono- and dichorionic (MC and DC, respectively) twins are reported to be up to six times higher than in singleton pregnancies and occurs in about 1% of all twin pregnancies[1, 3, 5, 7]. A study hypothesizes that the increased prevalence of CHD in twins is mostly due to hemodynamic factors[5]. However, the number varies considerably according to population and study design, but to our knowledge, no one has investigated the prevalence of mCHD in both MC and DC twins after excluding cases with twin-to-twin transfusion syndrome (TTTS) [3, 5, 8, 9]. TTTS occurs in 9-15% of MC pregnancies with imbalanced blood flow through intertwin anastomoses in the shared placenta and can lead to cardiovascular disease in the fetuses [10]. A high prenatal DR of mCHD may improve the postnatal outcome [11-14] and also allow the possibility of genetic testing as CHD is associated with genetic aberrations[15, 16]. Moreover, prenatal detection enables prenatal counseling to support the couples' reproductive autonomy by providing detailed information about the cardiac condition, treatment options, and long-term prognosis, which in twin pregnancies also includes the option of selective feticide of the affected fetus. However, prenatal ultrasound screening in twins can be more difficult due to shadows from the co-twin and suboptimal views. Conversely, intensive monitoring of MC pregnancies may increase mCHD DR. Whether this affects the prenatal DR of mCHD in twins in our current screening setting is unknown.

Therefore, this study aimed to investigate the prevalence and DR of mCHD in twin pregnancies without acquired CHD secondary to TTTS in a nationwide unselected population following a standardized prenatal screening program.

METHODS

Data were retrieved in the fall of 2021 from The Danish Fetal Medicine Database (DFMD) and included all twin pregnancies in Denmark with a due date between the 1st of January 2009 and the 31st of December 2018, where at least one fetus/child had a CHD diagnosis. The total number of twin pregnancies and births from the same period was retrieved from Statistics Denmark [17]. In Denmark, all patients are identified by a personal registration number given at birth [18], and in the DFMD, the mother's identification number is linked to the child's identification number. The DFMD contains information on prenatal findings in all pregnancies with a first and/or second-trimester ultrasound screening as well as information on pregnancy and outcomes, including information on pre- and postnatally diagnosed structural anomalies, based on ICD-10 codes. The postnatal data in the DFMD are captured from the National Patient Registry, which on a personal level includes all ICD-10 diagnosis codes ever given to patients in the public healthcare system [19]. Exclusion criteria were: 1) singleton pregnancies misclassified as twins; 2) MC twin-pregnancies with twin reversed arterial perfusion (TRAP) or TTTS; 3) cases lost to follow-up; 4) pregnancies where validation could not confirm a mCHD diagnosis; 5) pregnancies with minor CHD; 6) pregnancies with unspecific diagnoses, and lastly; 7) duplicated pregnancies.

In Denmark, all pregnant women are offered participation in a prenatal screening program that includes two ultrasound scans performed in obstetric departments by FMF-certified sonographers (midwives and nurses): A first-trimester scan which includes dating by crown-rump length (CRL), risk assessment for common trisomies, and determination of chorionicity by the presence of single or two separate placentae and the presence of the "T-sign" or "lambda sign" of the intertwin membrane in case of a twin pregnancy; and a mid-trimester scan for assessment of growth and anatomy.

The national guideline for the second-trimester anomaly scan specifies the scanning protocol that contains an exam of the fetal heart including rhythm and location of the heart in the thorax, sizes of the atria and ventricles, location of the valves, outflow tracts, and location and size of the great vessels. The anatomical structures of the heart are examined through the following axial planes: the location in the thorax, the 4-chamber view, views of the right and left outflow tract, and the 3-vessel trachea view[20]. However, the current guideline was not introduced until around 2010. Before, the guideline only required the 4-chamber view. When a CHD is suspected at any time during the pregnancy, the woman is referred to a fetal medicine specialist, and if confirmed, referred to a fetal cardiologist.

All MC twin pregnancies are offered an early malformation scan including a fetal heart scan, around 15-16 weeks of gestation, and from there an ultrasound scan every second week performed by either a specially trained sonographer or a fetal medicine specialist. Complicated MC pregnancies are referred to one of the five highly specialized hospitals for surveillance (such as TTTS, malformations, twin anemia-polycythemia sequence, selective growth restriction, and death of the co-twin)[21]. Uncomplicated DC twin pregnancies are seen every fourth week from gestational week 18 by a sonographer. More than 95% of all Danish pregnant women attend the offered screening program[22].

Baseline characteristics of the study population were also retrieved from the DFMD and included maternal age at the first-trimester screening, parity, maternal BMI, chorionicity, smoking status, mode of conception, estimated date of delivery, gestational age at the mid-trimester scan, and gestational age at delivery.

We included all twin pregnancies with mCHD defined as structural abnormalities of the heart and great vessels requiring surgery within the first year of life – excluding ventricular septal defects due to the wide range of severity depending on the type and size. The included

diagnoses were as follows and were given at any point during the pregnancy or postnatally: 1) aortic atresia; 2) aortic valve stenosis; 3) aortopulmonary window; 4) atrioventricular septal defect (AVSD); 5) coarctation of the aorta; 6) double outlet right ventricle (DORV); 7) Ebstein's anomaly; 8) ectopia cordis; 9) hypoplastic right heart syndrome; 10) hypoplastic left heart syndrome; 11) pulmonary atresia; 12) tetralogy of Fallot (TOF); 13) total anomaly of the pulmonary venous return (TAPVR); 14) transposition of the great arteries (TGA); 15) common arterial trunk[1, 7].

All fetal medicine departments in Denmark use Astraia (Astraia GmbH, Munich) for image storage and fetal medicine database. All retrieved pregnancies from the DFMD were validated in the local Astraia databases regarding prenatal diagnoses as well as in the electronic healthcare records regarding postnatal diagnoses (Epic or Systematic) at the four referral centers for pediatric cardiology in Denmark (Odense University Hospital, Copenhagen University Hospital, Rigshospitalet, Aarhus University Hospital, and Aalborg University Hospital). Cases with a termination of pregnancy or intrauterine death were validated through autopsy reports where available. If a fetus with prenatally diagnosed mCHD had died before birth and no autopsy had been performed, the case was considered detected.

The following prenatal data were validated for each set of twins: estimated date of delivery assessed by ultrasound, chorionicity, time of diagnosis (gestational age at prenatal diagnosis, or postnatal), and the diagnoses that were given. The following postnatal data were extracted from the electronic patient files for each set of twins: Information on the outcome of the pregnancy, the age at CHD-related surgery or intervention, and the postnatal diagnoses. In cases with more than one mCHD diagnosis, the most severe diagnosis was registered, and each case was only included once.

The data were analyzed in R-studio version 3.6.1, and the results are listed as frequencies (*n*) with percentages (%), means with standard deviations (SD), or medians with interquartile ranges (IQR), where appropriate. Comparisons of baseline characteristics were made between the detected and undetected cases of mCHD using Pearson's Chi^2 test, Student's *t*-test, and the Wilcoxon Rank test, where appropriate, and results are given as *p*-values (significance level of 0.05). The prevalence of mCHD is presented per pregnancy, per fetus, and live-born twin. The prenatal DR of mCHD in twins is presented per fetus/child as percentages with 95% confidence intervals (CI) both for the entire cohort and per diagnosis.

The study was approved by the Danish Data Protection Agency (P-2021-460) and the Danish Patient Safety Authority (R-21031193). Data was administrated accordingly to the rules of the Danish Data Protection Agency.

RESULTS

We retrieved a total of 889 supposedly twin pregnancies with CHD from the DFMD. After excluding pregnancies according to our criteria, 59 pregnancies (60 fetuses) with mCHD were included in the study (Figure 1). In the same period, 12,722 twin gestations (25,444 fetuses) were registered in the DFMD resulting in a prevalence of mCHD of 4.6 per 1,000 twin pregnancies or 2.4 per 1,000 fetuses. Of the 60 fetuses, 42 were live-born. With 22,640 live-born twins in the same period, the prevalence of mCHD was 1.9 per 1,000 live-born twins. For comparison, the prevalence of mCHD, when including cases with TTTS (n=18), was 6.1 per 1,000 twin pregnancies or 3.1 per 1,000 fetuses. Of the 12,722 twin pregnancies from the same period, 10,211 were DC and 2,511 were MC. Thus, the prevalence of mCHD in DC pregnancies was 3.6 per 1,000 pregnancies and 9.2 per 1,000 MC pregnancies without TTTS (p=0.001).

A total of 41 fetuses from 40 pregnancies had a prenatally detected mCHD resulting in a DR of 68.3% (41/60) (95% CI: 0.56-0.79). We included two mCHD diagnoses that are usually not screened for (TAPVR and aortopulmonary window, n=2). When excluding these two cases, the prenatal DR of mCHD was 70.7% (41/58). The DR for MC twins was 82.6% (95% CI: 61.2-95.1) and for DC twins 59.5% (95% CI: 42.1-75.3) (p=0.06). We excluded 18 MC pregnancies with major CHD and TTTS, where the cardiac complications in the recipient had all been detected.

Of the 41 fetuses with a prenatally detected mCHD, the diagnosis was validated at birth in 24 cases and by autopsy in one case (termination of the whole pregnancy). In the remaining 16 fetuses, selective feticide or termination of the pregnancy was performed or the fetus died intrauterine without any autopsy performed. A total of 13 cases were detected before 18 weeks gestation, 21 cases between 18+0 and 22+6, and 7 cases were not detected until after 23 weeks

gestation. The median GA at detection was 133 days (IQR 114-147) for MC twins and 141 days (IQR 136-148) for DC twins, (p=0.6).

Baseline characteristics for the prenatally detected cases compared to the postnatally detected cases are presented in Table 1, the two groups were overall comparable. However, the median BMI of the mothers was 23 kg/m^2 in the prenatally detected group vs. 27 kg/m^2 in the postnatally detected group (p=0.02). In the detected group, 8.1% (3/37) of the mothers had a BMI of 30 kg/m^2 or more versus 16.7% (3/18) in the postnatally detected group (p=0.34).

In the 41 fetuses with a prenatal diagnosis, the diagnostic precision was 97.6% (40/41) with discordance between the pre- and postnatal diagnoses in one fetus, where TOF was diagnosed prenatally as a common arterial trunk. The case was included as prenatally detected mCHD though the exact diagnosis was not reached. If only including validated cases, the diagnostic precision was 96% (24/25).

The included mCHD diagnoses and the type-specific DRs are shown in Table 2. The DRs varied depending on the diagnosis with the highest DRs found in cases with univentricular hearts, common arterial trunk, ectopia cordis, and pulmonary atresia (100%), where none of the cases with TAPVR and Ebstein's anomaly were detected (0/1 and 0/1, respectively).

DISCUSSION

In this study covering 10 years in a nationwide cohort with a standardized, free-of-charge prenatal screening program, we found the prevalence of mCHD in twins to be 2.4 per 1,000 fetuses or 1.9 per 1,000 live-born twins, and the prenatal DR of mCHD in twin pregnancies to be 68.3% in cases without TTTS. Both the prevalence and the DR were higher in MC pregnancies compared to DC pregnancies, but the difference in DR did not reach statistical significance. Moreover, we found a significantly higher BMI in the mothers in the undetected compared to the detected group.

The prevalence of mCHD in DC twins and MC twins without TTTS has not previously been estimated. The prevalence of CHD in twins in other studies is higher than the prevalence of CHD in our study (0.7-2.0% of live births) [2, 3, 5]. However, these studies are older and included minor CHD as well as cases with mCHD secondary to TTTS. The pre- and postnatal mCHD diagnoses from registers in Denmark have previously been validated in singletons [23]. The lower prevalence found in the present study is most likely a result of the standardized first-trimester screening that makes early termination of pregnancy or selective feticide a reproductive choice in case of conditions associated with mCHD (i.e. chromosomal anomaly or a very large nuchal translucency) before the diagnosis of a CHD is easily made. In Denmark, more than 95% terminate pregnancies with Trisomy 21 [24]. Overall, the reported prevalence of mCHD in twins was comparable to the prevalence of mCHD in singletons in Denmark from the same period[1, 23]. The prevalence of mCHD was higher in MC twins compared to DC twins, which has also previously been described[5].

The prenatal DR of mCHD in Denmark has previously only been evaluated in singleton pregnancies[1, 23, 25]. A large, national study on singletons from 1996 to 2013 found an increasing DR from 4.5% in 1996 to 71% in 2013[1]. The DR in twins found in this present study was

68.3%. However, the singleton study did not include TAPVR and aortopulmonary window, hence a more correct DR from the current study used for comparison is 70.7%. Consequently, we found the Danish DRs in singleton and twin pregnancies to be overall comparable. However, the periods examined differ and the 3-vessel and tracheal view was not included in the guideline until around 2010.

Twin pregnancies might be more difficult to scan; conversely, they follow a maternal and fetal surveillance program with more frequent ultrasound assessments than singletons. We have not been able to identify other, international publications focusing solely on mCHD in twin pregnancies, but many studies of mixed populations of CHDs [3, 5, 8, 26-29]. The results from these studies vary greatly, which may be due to different and smaller populations, but also available equipment, training, and guidelines [8, 26]. The study populations in these studies also differ from this current study, as all of them have included twins with TTTS. We found a higher DR in MC pregnancies and an earlier GA at diagnosis, though not significant, possibly due to small numbers. The difference could be explained by 1) an early malformation scan at 16 weeks in MC pregnancies, 2) closer ultrasonographic surveillance of MC pregnancies with 3) a focus on the fetal circulation and heart due to the risk of TTTS in those pregnancies. The DR of coarctation of the aorta was 25% making it one of the lowest DRs. Though, coarctation is for several reasons difficult to detect prenatally and our DR is comparable to other studies with DRs of 23.5-27.1%[1, 25]. However, it has been shown possible to improve prenatal detection using the isthmal Z-scores and isthmal-to-ductal ratio in cases suspected of coarctation[30, 31].

Prenatal diagnosis of mCHD is important as this enables optimization of delivery and postnatal treatment and is associated with increased neonatal survival for some diagnoses [11-14]. The DR of the different mCHD diagnoses varied from 0 to 100% in the present study. All cases of univentricular hearts were detected prenatally, which is of importance as most cases with this

disease requires immediate postnatal treatment [32], and even with optimal treatment, these children are at higher risk of both brain injury and developmental delay [33-35]. Hence, prenatal detection is also important for parental decision-making.

We found a significantly higher maternal BMI in the group with prenatally undetected mCHD (compared to the group with prenatally detected CHD). Obesity is a well-known challenge to prenatal ultrasound by decreasing image quality and hence accuracy, thus potentially resulting in non-detected anomalies in the fetus such as CHDs [36, 37]. In contrast to our results, other studies on the DR of CHD have found no or little effect of maternal obesity, but these studies were performed on singleton pregnancies only or only included three cases of missed CHD diagnosis in twins [38, 39]. Challenges due to high BMI might be overcome by transvaginal ultrasound if the fetal position allows it, and also by offering an early anomaly scan [40].

This study has several strengths. It is a nationwide study with more than 95% of pregnant women attending a standardized screening program. Furthermore, data are prospectively collected with a very high proportion of complete postnatal follow-ups. Lastly, all diagnoses in this study were both pre- and postnatally validated. As for limitations, despite many pregnancies resulting in termination or selective feticide, an autopsy was only performed in one case. We assumed the other cases to be correctly diagnosed, which might result in an overestimation of the diagnostic precision. Due to mCHD being a rare condition, our number of included cases is relatively low with very low numbers for individual lesions, thus wide confidence intervals. Further, postnatal diagnoses could be missing in the retrieved data from the DFMD. However, in singletons, we have previously found 100% concordance between postnatal CHD diagnoses in the DFMD and the patient files[23]. Two cases with unspecific mCHD diagnosed early were excluded. They both had multiple malformations and severe growth restriction and the parents opted for selective feticide before an exact diagnosis had

been given. They were both detected; hence, the DR presented here might be slightly underestimated, as is the prevalence (4.6 versus 4.8 per 1,000 twin pregnancies). We have compared the prevalence of mCHD in twins to singletons from already published studies rather than including the singletons in this study. Though this may introduce a bias, the methods and periods were similar, and the prevalences found in the two historical cohorts were similar.

In conclusion, in a nationwide 10-year twin cohort without CHD secondary to TTTS following a standardized prenatal screening program, we found the prevalence of mCHD to be 2.4 per 1,000 fetuses. The prevalence was higher in MC twins compared to DC twins. The DR of mCHD was 68.3%, which is also comparable to singleton studies. Moreover, the BMI of the mothers was significantly higher in the undetected compared to the detected group.

ACKNOWLEDGMENT

Professor Olav Bjørn Petersen holds a professorship, funded by The Novo Nordisk Foundation grant NNFSA170030576.

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FIGURE LEGEND

Figure 1: Flowchart of the study population

Table 1: Baseline characteristics of mothers expecting twins with congenital heart defects and comparison between prenatally detected and undetected cases.

	Detected n=41	Postnatally detected n=19	*P*-value
Maternal age at first-trimester scan (years)	32 (29-36)	32 (30-36)	0.91
Nulliparous Missing	13 (31.7) 6 (14.6)	9 (47.4) 5 (26.3)	0.09
Chorionicity - Dichorionic - Monochorionic	 22 (53.7) 19 (46.3)	 15 (78.9) 4 (21.1)	0.06
Pre-gestational BMI (kg/m^2) Missing	23 (21-26) 4 (9.8)	27 (23-29) 1 (5.3)	0.02
Maternal smoking, yes Missing	2 (4.9) 4 (9.8)	1(5.3) -	0.98
Spontaneous conception Missing	25 (61.0) 4 (9.8)	9 (47.4) 1 (5.3)	0.22
Gestational age at birth (days) Missing (termination of pregnancy)	261 (239-266) 3 (7.3)	260 (243-267) -	0.88

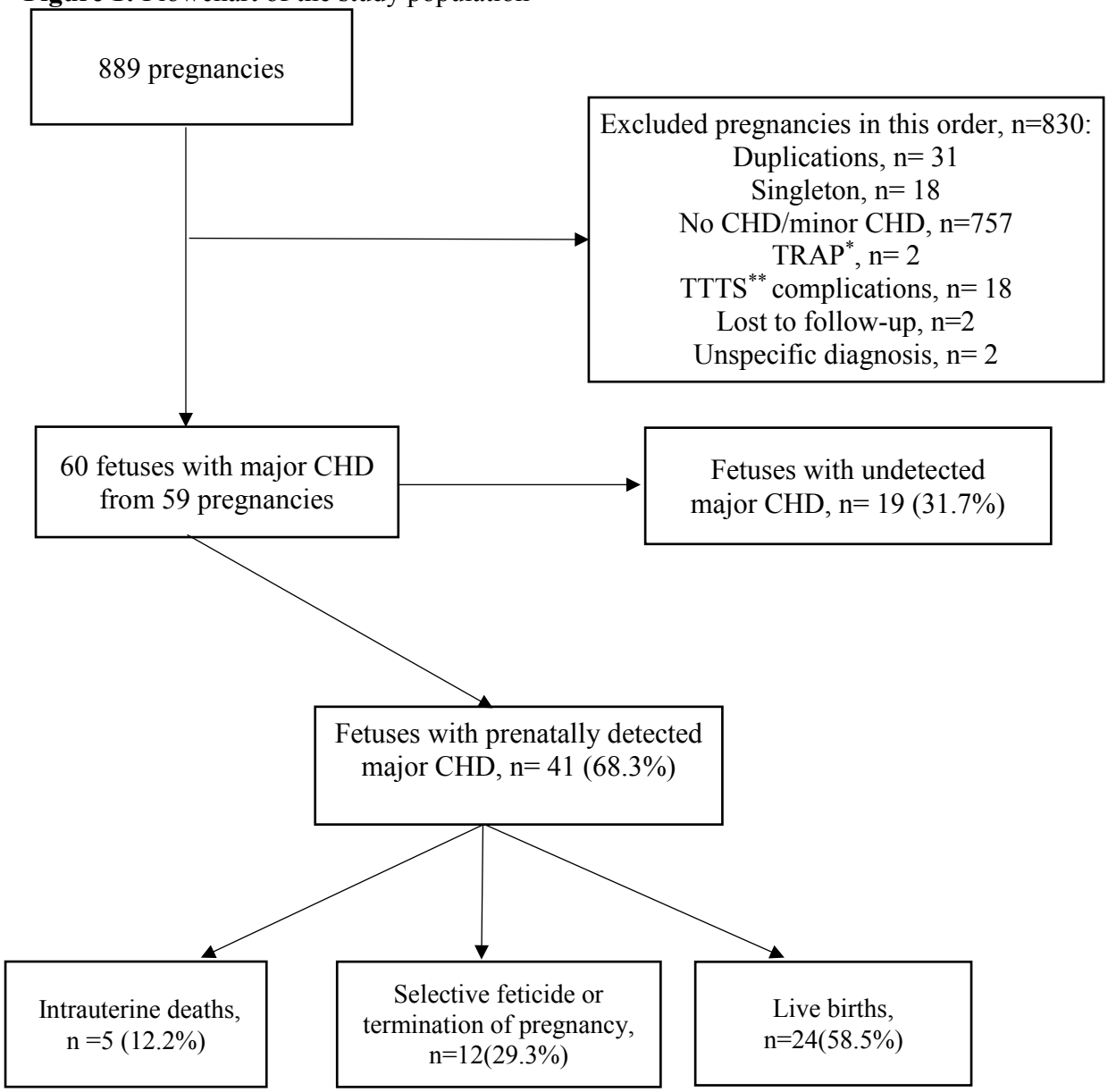
Data are given as median (interquartile range) or n (%).

Table 2: Included diagnoses, total numbers, and the prenatal detection rates. Listed alphabetically.

Congenital heart disease	Number of included fetuses (% of total number of affected fetuses)	Number of detected cases (per fetus) prenatally	Prenatal detection rate % (95% CI)
Aortic valve stenosis	4 (6.6)	1	25 (0.6-80.6)
Aortopulmonary window	1 (1.7)	0	0 (0.0-97.5)
Atrioventricular septal defect	4 (6.6)	3	75 (19.4-99.4)
Coarctation of the aorta	8 (13.3)	2	25.5 (3.2-65.1)
Double outlet right ventricle	2 (3.3)	1	50 (1.3-98.7)
Ebstein's anomaly	1 (1.7)	0	0 (0.0-97.5)
Ectopia cordis	2 (3.3)	2	100 (15.8-100.0)
Hypoplastic left heart syndrome	10 (16.7)	10	100 (69.2-100.0)
Hypoplastic right heart syndrome	6 (10)	6	100 (54.1-100.0)
Pulmonary atresia	1 (1.7)	1	100 (2.5-100.0)
Tetralogy of Fallot	10 (16.7)	8	80* (44.4-97.5)
Total anomaly of the pulmonary venous return	1 (1.7)	0	0 (0.0-97.5)
Transposition of the great arteries	9 (15)	6	66.6 (29.9-92.5)
Common arterial trunk	1 (1.7)	1	100 (2.5-100.0)
In total	**60 (100)**	**41**	**68.3 (55.0-79.7)**

*One patient with postnatally diagnosed TOF was prenatally diagnosed with common arterial trunk. This case was classified as detected.

Figure 1: Flowchart of the study population



*TRAP, twin reversed arterial perfusion
**TTTS, twin-twin-transfusion syndrome