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CLINICAL RESEARCH

Prognosis of severe congenital heart diseases: Do we overestimate the impact of prenatal diagnosis?

Pronostic des cardiopathies congénitales sévères : surestimons-nous l'impact du diagnostic prénatal ?

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Summary
Background. — Prenatal diagnosis of congenital heart disease (CHD) is controversial because of unclear benefits in terms of morbidity and mortality, and issues with healthcare costs and organization.
Aim. — To compare, in children with severe CHD, 1-year morbidity and mortality between prenatal and postnatal diagnosis groups.

Abbreviations: CHD, Congenital Heart Disease; TGA, Transposition of the Great Arteries; TOP, Termination Of Pregnancy.

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Methods. — All pregnancies and children aged < 1 year with a diagnosis of severe CHD were collected over a 5-year period from our database. Severe CHDs were defined as lethal cases, cases leading to medical termination of pregnancy, or children requiring surgery and/or interventional catheterization and/or hospitalization during their first year of life. The primary endpoint was 1-year mortality rate among live births.
Results. — Overall, 322 cases of severe CHD were identified; 200 had a prenatal diagnosis and there were 97 terminations of pregnancy. Of the 225 live births, 34 died before the age of 1 year. The 1-year mortality rate was not significantly different between prenatal and postnatal groups (16.7% vs. 13.9%; $p = 0.13$). In the prenatal group, prostaglandin use was more important and precocious, duration of hospitalization stay was longer, extracardiac complications were less common and cardiac surgery was performed more frequently and later. An association with chromosomal or syndromic anomalies was a risk factor for 1-year mortality.
Conclusions. — Prenatal diagnosis of severe CHD had an impact on the decision regarding termination of pregnancy, but not on the 1-year prognosis among live births. We should now use large multicentre CHD registries to determine the impact of prenatal diagnosis on postnatal management, neurological prognosis and quality of life.

MOTS CLÉS
Échographie ;
Mortalité ;
Cardiopathie congénitale ;
Morbidité ;
Pédiatrie

Résumé
Contexte. — L'intérêt du diagnostic prénatal des cardiopathies congénitales (CC) oppose l'impact incertain sur la morbi-mortalité aux enjeux médicoéconomiques.
Objectif. — Cette étude a comme objectif de comparer, chez les enfants atteints de CC, la morbi-mortalité à un an entre les groupes avec et sans diagnostic prénatal.
Méthodes. — Nous avons recueilli sur 5 ans les CC sévères chez les femmes enceintes et enfants âgés < 1 an. Les CC sévères concernaient les décès, interruptions médicales de grossesse (IMG), le recours à une chirurgie, un cathétérisme interventionnel ou une hospitalisation au cours de la première année de vie. Le critère principal de jugement était la mortalité à un an parmi les naissances vivantes.
Résultats. — 322 CC sévères ont été inclues, dont 200 diagnostics prénataux et 97 IMG. Sur les 225 naissances vivantes, 34 sont décédées avant l'âge d'un an. La mortalité à un an n'était pas significativement différente entre les groupes prénatal et postnatal (16,7 % vs 13,9 % ; $p = 0,13$). Dans le groupe prénatal, l'utilisation de prostaglandines était plus importante et précoce, la durée d'hospitalisation plus longue, les complications extracardiaques moins fréquentes et la chirurgie cardiaque plus fréquente et plus tardive. L'association à des anomalies chromosomiques ou syndromiques était un facteur de risque de mortalité à un an.
Conclusions. — Le diagnostic prénatal de CC sévère a un impact sur la décision d'IMG, mais pas sur le pronostic à un an parmi les naissances vivantes. De larges registres multicentriques de CC devront déterminer l'impact du diagnostic prénatal sur la prise en charge postnatale, le pronostic neurologique et la qualité de vie.

Background

Congenital heart disease (CHD) is the most common of all birth defects, accounting for about 8 in 1000 births [1]. The prevalence of prenatally diagnosed CHDs has risen progressively over the past decade, but the effect that prenatal diagnosis of CHD has on morbidity and mortality among live births remains unclear [2].

In many countries, prenatal diagnosis is stratified into three levels of expertise. The mass ultrasound screening of all pregnancies is performed by a trained obstetrician or midwife at approximately 12, 22 and 32 weeks of gestation. In case of any suspicion of malformation, the patient is referred to an expert sonographer in a prenatal diagnosis centre. Finally, if CHD is diagnosed according to international guidelines [3,4], the patient is referred to a paediatric cardiologist with expertise in fetal cardiology, usually in a CHD tertiary care centre.

Theoretically, prenatal diagnosis aims to improve neonatal outcome, detect associated chromosomal or syndromic diseases and facilitate discussion of termination of pregnancy (TOP) with the parents for the most severe CHDs.

Accessibility and timing of TOP vary between countries [1,5]. In France, TOP is legally authorized for medical reasons until the end of pregnancy. France has promoted fetal diagnosis since the early 1980s; consequently, it has high rates of prenatal diagnosis [5,6]. However, access to TOP and prenatal diagnosis has not significantly modified the neonatal incidence of CHD in France, which is still similar to that of most other countries [1].

In addition, several studies have identified controversies regarding prenatal diagnosis. Benefits in terms of morbidity and mortality remain unclear. Most studies found no significant difference in early (before maternity leave) or late (at 1, 2 and 5 years) survival, postoperative complications and duration of hospitalization [7—10]. Some studies even reported a lower survival rate at 6 days [7] or 28 days [9] in patients with prenatal diagnosis. Moreover, prenatal diagnosis has been stigmatized substantially as a time- and cost-consuming healthcare activity. Pinto et al. pointed out a higher duration (13 additional days) and cost ($90,419 vs. $49,576) of neonatal hospitalization in prenatally diagnosed cases of transposition of the great arteries (TGA) [11]. The psychological effects on the child's family must also be taken into consideration, as more cases of maternal anxiety, stress or depressive status have been reported in prenatal diagnosis groups [12—14]. Lastly, some studies mentioned medicolegal issues [15] and an increase in invasive procedures, such as amniocentesis [16], related to prenatal diagnosis.

Many studies investigating the impact of prenatal diagnosis included the least severe CHDs, such as ventricular septal defect or valvular pulmonary stenosis, and did not consider some important sources, such as sudden infant death registries.

Therefore, we aimed to compare, from a tertiary care CHD database, 1-year morbidity and mortality rates between prenatal or postnatal diagnosis groups, in children with severe CHD.

Methods

Study design and population

We included all cases of severe CHD diagnosed over the last 5 years (January 2013 to January 2018) in our tertiary care paediatric and congenital cardiology department (Montpellier University Hospital, France), either during pregnancy or in children aged < 1 year. We defined severe CHD as follows: lethal cases; cases leading to medical TOP; or children requiring heart surgery and/or interventional catheterization and/or hospitalization for heart failure during the first year of life. All severe or complex CHD cases in the Languedoc-Roussillon region, in the south of France, are diagnosed in our tertiary care CHD centre (M3C regional reference centre). Moreover, all sudden infant deaths occurring in that region benefit from a mandatory autopsy in our institution.

We excluded cases of TOP if the diagnosis was not confirmed by the autopsy, patients with cardiomyopathy, ductus arteriosus, atrial septal defect and cardiac tumour or arrhythmia.

We collected retrospectively descriptive and analytical data from medical records of pregnant women and neonates, as well as the autopsies for sudden infant deaths. The type of CHD was defined according to the International Classification of Diseases (ICD 10). We also classified CHDs according to ductal dependency (pulmonary or systemic circulation depending on ductus arteriosus) or mixing dependency (parallel circulation requiring interatrial and interarterial shunts to maintain sufficient oxygenation). We collected information about extracardiac complications requiring hospitalization during the first year of life: neurological event (convulsive seizure, stroke); infection; or respiratory distress (bronchiolitis, lung infection).

Maternal care facilities within the maternity unit were specified as follows: no neonatal unit (level 1); local neonatal unit (level 2); or neonatal intensive care unit (level 3).

Endpoints

The primary endpoint was the 1-year mortality rate among live births. We also assessed the following morbidity criteria at 1-year follow-up: medical treatment, such as prostaglandin, inotropic drugs, oxygen and assisted ventilation; time to surgical repair or interventional catheterization; occurrence of extracardiac complications causing or increasing duration of hospitalization; overall duration of hospitalization; and child growth. Postnatal evolution at 1 year was also assessed as follows: low severity for repaired CHD without residual lesions; moderate severity for repaired CHD with residual lesions; and high severity for palliative therapy or death.

Finally, to compare our study with previous literature results, we evaluated the accuracy of the prenatal diagnosis using two criteria. First, the accuracy of prenatal diagnosis was classified as ''exact'', ''minor variations not changing therapeutics'' or ''major variations changing therapeutics''. Second, the prognosis estimated during prenatal period was compared with the actual postnatal evolution at 1 year. The prenatal prognosis was estimated as follows: ''good prognosis'' when the disease required only one intervention with good results (e.g. ventricular septal defect); ''undefined prognosis'' when the prognosis was poorly assessed during the prenatal period because of important prognostic variations in the disease (e.g. Ebstein's anomaly); and ''bad prognosis'' for diseases with no curative therapy (such as univentricular heart defects).

Statistical analysis

Quantitative data are expressed as means ± standard deviations or medians [minimum-maximum or interquartile range]. Qualitative data are described as numbers and percentages. Comparisons between groups were performed using the χ^2 test or Fisher's exact test, as appropriate, for qualitative variables or mean comparison tests (Student's or Wilcoxon depending on the distribution) for quantitative variables.

Multivariable analysis (logistic regression) was performed to highlight the respective influence of each covariate on the endpoint studied, i.e. 1-year mortality rate. Adjusted odds ratios and 95% confidence intervals were calculated.

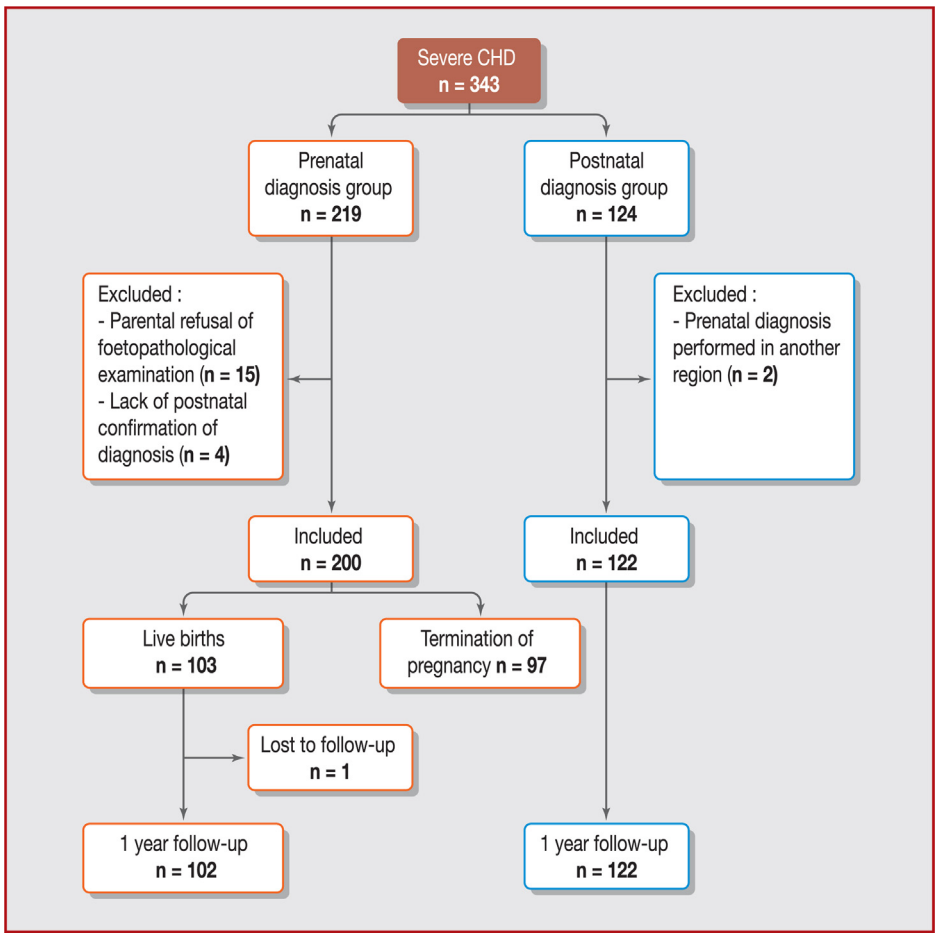

Figure 1. Flow chart. CHD: congenital heart disease.

Finally, we applied propensity score models to correct selection bias in our two groups. A number of ''points'' (propensity score) was attributed to each subject according to the severity of the pathology: one point for each factor associated with 1-year mortality risk in the univariate analysis (e.g. intrauterine growth restriction, ductal or mixing dependency, neonatal acidosis, desaturation or intubation, amine use before surgery, cardiac surgery or catheterization). Group adjustments and comparison between groups were made after stratification of risk: zero points = low mortality risk group; one point = average mortality risk group; two or more points = high mortality risk group.

The significance level was set at 5% for all tests used. Statistical analysis was performed with SAS software, version 9 (SAS Institute, Cary, NC, USA).

Results

Population

A total of 343 cases with severe CHD were identified; all were born or had a medical TOP within the study period. We excluded 19 foetuses from the analysis as a result of missing anatomical diagnosis. Finally, 322 patients were included: 200 in the prenatal diagnosis group and 122 in the postnatal diagnosis group (Fig. 1).

TOP concerned 48.5% of the prenatal group (97/200); the most frequent medical indications for TOP were univentricular heart defects (47.2%), severe valvular diseases (23.8%) and CHD associated with chromosomal anomalies (16.5%).

The characteristics of the live birth population (TOP excluded), including the type of CHD, are described in Table 1. Our cohort had a male preponderance (60.9%), and a significant number of premature births (14.7%) and twin pregnancies (6.2%). Maternal mean age at the beginning of pregnancy was 29 ± 6 years. For three children (2.5%), the diagnosis of CHD was performed during an autopsy (sudden infant death registry): one with hypoplastic left heart syndrome (sudden death on maternity ward at first day of life); one with total anomalous pulmonary venous return (death at home at 7 days of life); and one with coarctation of the aorta (death at home at 5 days of life).

Of all cases of severe CHD, 62.1% (200/322) had a prenatal diagnosis. The mean term at diagnosis was 24 ± 5 weeks of gestation.

Morbidity and mortality outcomes

When considering the 225 live births, we found no significant difference between prenatal and postnatal diagnosis groups in terms of the 1-year mortality endpoint (Table 2). Parents and healthcare professionals elected cardiac surgery for all children in this group. Of the 225 live births, 34 (15.2%)

Table 1 Live birth characteristics after prenatal and postnatal diagnosis of congenital heart disease.

Live births (TOP excluded)	Total ($n = 225$)	Prenatal diagnosis ($n = 103$)	Postnatal diagnosis ($n = 122$)	*P*
Male sex	137 (60.9)	62 (60.1)	75 (61.4)	0.84
Term of birth (WG)	39 [25—42]	39 [27—42]	39 [25—42]	0.89
Premature birth (< 37 WG)	33 (14.7)	13 (12.6)	20 (16.3)	0.43
Weight at birth (g)	3110 [480—4500]	3080 [480—4390]	3140 [600—4500]	0.82
Twins	14 (6.2)	6 (5.8)	8 (6.5)	0.82
Apgar score at 5 minutes	9.2 [0—10]	9.4 [1—10]	8.9 [0—10]	< 0.001
Chromosomal anomaly	67 (29.7)	32 (31.1)	35 (28.8)	0.7
Age at CHD diagnosis				
In WG	—	24 [17—41]	—	NA
In days	—	—	5 [0—350]	NA
Maternal age (years)	29 [18—44]	29	29.5	0.73
Type of CHD				
Large VSD	52 (23.1)	11 (10.7)	41 (33.6)	< 0.001
TGA	35 (15.6)	23 (22.3)	12 (9.8)	0.01
Coarctation of aorta	34 (15.1)	11 (10.7)	23 (18.9)	0.09
Tetralogy of Fallot	21 (9.3)	14 (13.6)	7 (5.7)	0.04
AVSD	11 (4.9)	8 (7.8)	3 (2.5)	0.12
DORV	10 (4.4)	7 (6.8)	3 (2.5)	0.19
HLHS	9 (4.0)	8 (7.8)	1 (0.8)	0.01
TAPVD	7 (3.1)	1 (1.0)	6 (4.9)	0.13
Pulmonary stenosis	6 (2.7)	0 (0)	6 (4.9)	0.03
Tricuspid atresia	4 (1.8)	3 (2.9)	1 (0.8)	0.33
Ebstein's anomaly	4 (1.8)	4 (3.9)	0 (0)	0.04
Truncus arteriosus	4 (1.8)	2 (1.9)	2 (1.6)	1
Aortic stenosis	4 (1.8)	2 (1.9)	2 (1.6)	1
Others	22 (9.8)	9 (8.7)	13 (10.7)	0.66
Ductal dependency	70 (31.1)	35 (34.3)	35 (28.7)	0.01
Mixing dependency	34 (15.1)	22 (21.6)	12 (9.8)	0.01

Data are expressed as number (%) or median [minimum—maximum]. AVSD: atrioventricular septal defect; CHD: congenital heart disease; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; TAPVD: total abnormal pulmonary vein drainage; TGA: transposition of the great arteries; TOP: termination of pregnancy; VSD: ventricular septal defect; WG: weeks of gestation.

children died before the age of 1 year, at a median age of 21 [0—224] days. Death occurred before heart surgery in 24 cases (70.6%), after at least one cardiac surgical procedure in nine cases (26.5%, two-thirds of which were within 1 month after surgery) and during surgery in one case (2.9%). The highest postnatal mortality rate of 77.7% was found in patients with hypoplastic left heart syndrome (HLHS).

In the prenatal group, prostaglandin use was more frequent and occurred earlier, duration of hospitalization stay was longer, extracardiac complications were less common and cardiac surgery was more frequent and was performed later (Table 2).

Variables associated with 1-year mortality among live births in the univariate analysis are reported in Table 3. The 1-year mortality rate was higher in patients with ductal dependency, intrauterine growth restriction and catecholamine use before surgery.

All birth modality variables (planned delivery, vaginal birth or caesarean section, maternal birth level, distance from a CHD centre) were not associated with any increased mortality at 1 year, among live births.

In the multivariable analysis, the presence of a chromosomal anomaly and/or a malformation syndrome was the only factor associated with higher 1-year mortality among live births (odds ratio 4.17, 95% confidence interval 1.35—14.29).

The children in the prenatal diagnosis group were more affected by serious health conditions (Table 1). Therefore, CHDs with ductal dependency or associated with chromosomal abnormality and/or malformation syndrome were more common in the prenatal diagnosis group.

When adjusting the 1-year mortality risk with a propensity scale score analysis (ductal dependency, intrauterine growth restriction, association with chromosomal abnormality or malformation syndrome), we found no significant difference between groups in 1-year mortality among live births (Table 2).

Prenatal diagnosis accuracy

The postnatal evaluation confirmed the prenatal diagnosis accurately in 161 cases (80.5%), with minor variations resulting in no change to treatment in 32 cases (16%) and major variations in seven cases (3.5%).

Similarly, the CHD severity and prognosis defined during the prenatal period were consistent with the postnatal evolution (Table 4). All CHDs identified as ''with a severe

Table 2 Mortality and morbidity outcomes among live births in prenatal and postnatal diagnosis groups.

Morbidity and mortality outcomes	Prenatal diagnosis ($n = 103$)		Postnatal diagnosis ($n = 122$)		P
	n		n		
1-year mortality	102	17 (16.7)	122	17 (13.9)	0.13
1-year mortality risk[a]					
Low	53	0 (0)	61	2 (0)	0.30
Moderate	17	2 (10.5)	25	3 (10.7)	0.10
High	15	12 (44.4)	19	12 (38.7)	0.26
Prematurity	103	15 (14.6)	121	18 (14.9)	0.95
Growth restriction	103	16 (15.5)	122	15 (12.3)	0.48
Assisted ventilation	103	27 (26.2)	122	38 (31.2)	0.42
Catecholamine use before cardiac surgery	103	10 (9.7)	122	15 (12.3)	0.54
Prostaglandin use	102	46 (45.1)	122	28 (22.8)	0.001
Delay before prostaglandin use (days)	46	1.7 [0—20]	28	8.4 [0—47]	< 0.001
Cardiac surgery	102	84 (82.4)	122	86 (70.5%)	0.04
Delay before cardiac surgery (days)	84	131.1 [3—1404]	86	127.7 [1—689]	0.004
Complications after cardiac surgery (< 30 days)	84	44 (52.4)	86	38 (44.2)	0.29
Diagnosis cardiac catheterization	102	37 (36.3)	122	38 (31.1%)	0.16
Intervention cardiac catheterization	102	37 (36.3)	122	30 (24.6)	0.16
Delay before cardiac catheterization (days)	37	93.0 [0—1620]	30	138.2 [0.25—730]	< 0.001
Complications after cardiac catheterization (< 30 days)	58	11 (18.9)	59	5 (8.5)	0.10
1-year extracardiac complications	102	59 (57.8)	122	86 (70.5)	0.04
Duration of hospitalization at 28 days (days)	102	17.5 [0—35]	122	12.7 [0.25—29]	0.001
Duration of hospitalization at 1 year (days)	102	33.3 [0—30]	122	37.5 [0.25—221]	0.86
Weight at the age of 1 month (g)	95	3515 [1800—5300]	82	3551 [800—5256]	0.74

Data are expressed as number (%) or median [minimum—maximum].
[a] Mortality risk estimated with propensity score analysis.

prognosis'' (no curative therapy) in the prenatal period had a high severity at 1 year (palliative therapy or death). In case of a prenatal prognosis announced as ''undefined'' (significant doubt about the severity), the postnatal evolution was pejorative in half of the cases. When the prenatal prognosis was announced as ''good'', it underestimated the real severity in one in five cases.

Discussion

In this cohort of 225 children with severe CHD, 46% of whom were diagnosed prenatally, we found that prenatal diagnosis had no significant impact on the 1-year morbidity and mortality endpoints. This result was also confirmed after multivariable analysis and propensity scale analysis, despite a good prenatal diagnosis performance. Indeed, prenatal diagnosis groups are usually more severe than postnatal diagnosis groups because of the higher detection rate in the most severe CHDs. These results are in line with previous studies [7—10,17], as well as with a recent review of the literature [18], reporting a similar or poorer prognosis in the prenatal diagnosis population, regarding 1-month mortality or 1-year survival.

Nevertheless, some CHDs may benefit from an accurate prenatal diagnosis. For instance, TGA may require a specialized emergency neonatal procedure, with intervention catheter therapy (Rashkind's atrioseptostomy). Therefore, prenatal diagnosis allows a multidisciplinary delivery plan in a tertiary care CHD centre to be defined, which has been shown to improve prognosis in TGA [19,20]. Interestingly, in our study, the presence of a paediatric cardiologist at birth or a short distance between the maternity care facility and the CHD tertiary care centre did not affect the overall prognosis. Indeed, our regional network of obstetricians and paediatricians has drafted and published harmonized reference frames dedicated to all healthcare professionals involved in perinatal medicine [21]. For instance, non-expert professionals are trained to diagnose a ductal-dependent CHD, and to start prostaglandin before transferring the neonate to our tertiary care referral CHD centre.

Epidemiological studies on performance or impact of CHD prenatal diagnosis are usually difficult to compare. Indeed, results may vary significantly, depending on the type of the considered population (registries or hospital studies in a reference centre for prenatal diagnosis), the starting point of the study (prenatal diagnosis or confirmed cases after birth, sometimes before maternity leave), the spectrum of heart diseases included (all CHDs regardless of their severity, severe CHDs with several severity criteria, only one type of CHD, such as TGA or hypoplastic left heart syndrome) or the modalities of obstetric follow-up and access to TOP [22—25]. Unfortunately, the ideal study is not actually possible. We were therefore obliged to compare two populations (with prenatal diagnosis and without prenatal diagnosis) that may not be very comparable, especially when the antenatal

Table 3 Variables associated with 1-year mortality among the live birth population (termination of pregnancy excluded).

	Patients alive at 1 year of age ($n = 190$)	Patients dead before 1 year of age ($n = 34$)	*P*
Prenatal diagnosis	82 (43.9)	20 (54.1)	0.25
Premature birth (< 37 WG)	26 (14.0)	7 (18.9)	0.44
Intrauterine growth retardation	22 (11.8)	9 (24.3)	0.04
Ductal/mixing dependency			0.005
Ductal dependency	50 (26.9)	20 (54.1)	
Mixing dependency	31 (16.7)	3 (8.1)	
None	105 (56.5)	14 (37.8)	
Planned delivery	97 (51.9)	19 (51.4)	0.95
Maternal care facility[a]			0.17
Level 1	53 (28.3)	7 (18.9)	
Level 2	11 (5.9)	5 (13.5)	
Level 3	123 (65.8)	25 (67.6)	
Neonatal acidosis	2 (1.1)	10 (29.4)	< 0.001
Neonatal or preoperative intubation	43 (23.0)	22 (59.5)	< 0.001
Cardiac surgery	157 (84.0)	13 (35.1)	< 0.001
Cardiac catheterization			0.004
Diagnostic	55 (29.4)	6 (16.2)	
Interventional	49 (26.2)	4 (10.8)	
Both	13 (7.0)	1 (2.7)	
Amine use before surgery			< 0.001
None	177 (94.7)	22 (59.5)	
One	9 (4.8)	7 (18.9)	
Two or more	1 (0.5)	8 (21.6)	
Neonatal or preoperative transfusion	26 (13.9)	8 (22.2)	0.20
Presence of a paediatric cardiologist at delivery	107 (57.2)	22 (59.5)	0.80
Pacemaker	2 (1.1)	0 (0)	1.0
Neonatal saturation	98 [50—100]	88 [30—100]	< 0.001
Apgar score at 5 minutes	10 [5—10]	9 [0—10]	< 0.001
Distance from maternity care facility to CHD centre (km)	0 [0—150]	0 [0—120]	0.97
1-month weight (kg)	3.5 [0.8—5.3]	3.5 [1.9—4.2]	0.40
Age at first cardiac surgery (days)	39 [2—1404]	21 [1—828]	0.34
Duration of oxygen therapy (days)	0 [0—365]	1 [0—48]	< 0.001

Data are expressed as number (%) or median [minimum—maximum]. CHD: congenital heart disease; WG: weeks of gestation.
[a] Maternal care facilities: level 1: no neonatal unit; level 2: local neonatal unit; level 3: neonatal intensive care unit.

Table 4 Comparison between prenatal prognosis and 1-year postnatal evolution.

	n	Low severity at 1 year	Moderate severity at 1 year	High severity at 1 year
Good prenatal prognosis	71	40 (56.3)	17 (23.9)	14 (19.7)
Indeterminate prenatal prognosis	42	9 (21.4)	9 (21.4)	21 (50.0)
Severe prenatal prognosis	84	0 (0)	0 (0)	84 (100)

Data are expressed as number (%).

diagnosis becomes so efficient, with a TOP rate of nearly 50% in our study.

We voluntarily selected the most severe CHDs to reach the main objective of our study. Indeed, prenatal screening does not aim to diagnose all CHDs, but, above all, those with a severe prognosis. From the database of our national population registry (INSEE), 173,298 children were born alive in our region during the study period. Therefore, the incidence of severe CHD was 1.29 per thousand live births.

In our study, 62.1% of all severe CHDs (TOP included) were diagnosed prenatally, which is higher than in previous studies, ranging from 6.1% to 57% [22—25]. Indeed, the French tertiary care referral centres for complex CHD (M3C network) have rationalized prenatal diagnosis into three

levels of expertise. The performance of prenatal screening for CHD has therefore improved progressively over the last two decades. However, the mean term at prenatal diagnosis of CHD in this study was 24 weeks of gestation, which is late, given that an accurate diagnosis is possible from 18 weeks of gestation. In France, fetal ultrasonography is usually performed between 18 and 20 weeks of gestation, by an obstetrician with expertise in prenatal diagnosis. If a CHD is suspected, the patient is referred to a paediatric cardiologist with expertise in fetal ultrasonography, to confirm the diagnosis and organize the follow-up. Therefore, despite a high level of prenatal screening, the time to prenatal diagnosis still needs to be optimized within the M3C network.

Simultaneously, epidemiological studies have emphasized the transfer of mortality from infanthood to adulthood in complex CHDs [26]. The influence of prenatal screening in this new epidemiology remains unproven [27]. However, we cannot deny that prenatal diagnosis is probably related to improved neonatal management (early diagnosis, prostaglandin infusion, rapid transfer to an expert centre) and progress in surgical and anaesthetic management.

As a consequence of these controversial results, there is currently a debate about the benefit of CHD prenatal diagnosis: if there is no mortality impact, should we promote prenatal diagnosis? First, some CHDs are often associated with a chromosomal anomaly. In our study, this was a poor prognostic factor, which increased morbidity and mortality risks, as has been reported elsewhere [28]. Therefore, that aspect could improve parental information or lead to TOP or neonatal end-of-life palliative care [29]. Secondly, in our study, prenatal diagnosis was associated with more precocious management in terms of delay before introducing prostaglandin and delay before performing surgery or intervention catheterization. Moreover, the 1-year extracardiac complications (such as respiratory distress, infection or convulsions) were significantly less frequent in the prenatal diagnosis group.

Previous studies also reported an improvement in neonatal and preoperative clinical conditions: less heart or organ failure [9], less desaturation and heart failure [8] and less intubation, antibiotic therapy or urgent surgery [10] in the prenatal diagnosis group. However, different neurological complications are known to affect nearly 50% of children and adults with CHD: language delay, attention deficit hyperactivity disorder, impairment of fine motor skills, intelligence quotient, memory performance and visual-spatial acquisition [30—33]. Therefore, we can assume that prenatal diagnosis would facilitate earlier and safer management of severe CHD, which eventually might improve the long-term neurological prognosis.

Finally, the patient's quality of life stands today as a major ''patient-related outcome'' that is taken into consideration more and more in patients with CHD [34,35]. Further studies will need to measure the impact of prenatal diagnosis on the quality of life of patients with CHD.

Study limitations

This was a retrospective study, based on the experience of a single tertiary care referral CHD centre. However, by using multiples sources for data collection (prenatal diagnosis centre, paediatric cardiology department, anatomopathology department) we attempted to obtain exhaustive CHD data from a large region.

Despite a consistent total study population (225 + 97), our cohort presented great heterogeneity, with very different degrees of severity and smaller population sizes for each malformation. The analysis was carried out globally, on the whole population, but similar previous studies have shown that mortality rates are low and confidence intervals are wide in prenatal diagnosis of CHD.

Unfortunately, there is no ideal study design to demonstrate the real impact of CHD prenatal diagnosis. We could not apply a case-control design because of CHD complexity, CHD interindividual variability and the postnatal appearance of some CHDs (such as coarctation of the aorta).

Finally, the question of whether or not we overestimate the impact of prenatal diagnosis on the prognosis of severe CHD will probably remain unanswered for a long time. We may hypothesize that mortality is probably not a good indicator, and that it is currently necessary to join forces nationally and internationally to conduct multicentre studies.

Conclusions

Prenatal diagnosis did not improve the 1-year mortality endpoint in this cohort of 322 cases of severe CHD. However, in case of a prenatal diagnosis, immediate neonatal management protects from some morbidity factors, which could be associated with neurological sequelae. Prospective studies with relevant follow-up are required to evaluate the impact of prenatal diagnosis on neurological development and quality of life in the CHD population.

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Disclosure of interest

The authors declare that they have no competing interest.

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