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BMJ Open

Impact of prenatal diagnosis on survival of newborns with four congenital heart defects: a prospective, population-based cohort study in France (the EPICARD Study)

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ABSTRACT

Objectives (1) Assess the population-level probability of prenatal diagnosis and termination of pregnancy for fetal anomaly for four major congenital heart defects; (2) Examine, using population-based data, the relation between timing of (prenatal vs postnatal) diagnosis and risk of infant (ie, < 1 year) mortality for four major congenital heart defects (CHDs).

Design Population-based cohort (the EPIdémiologie des CARDiopathies congénitales) study.

Setting Greater Paris area (Paris and its surrounding suburbs).

Patients Three hundred and fifty-four cases of four major CHDs, including functionally univentricular heart (FUH, N=132), d-transposition of great arteries (d-TGA, N=85), tetralogy of Fallot (TOF, N=60) and coarctation of aorta (CoA, N=77). Statistical analysis included the Mantel-Haenszel method and a test of homogeneity of risk ratios.

Results Approximately 95% of FUH, more than two-thirds of d-TGA and TOF, and 40% of CoA were prenatally diagnosed. Overall, we did not find any statistically significant association between timing of (prenatal vs postnatal) diagnosis of CHD and risk of infant mortality (Mantel-Haenszel risk ratio 1.1, 95% CI 0.5 – 2.7); and the differences between the risk ratios of the association between prenatal diagnosis and infant mortality across the four CHDs was not statistically significant.

Conclusion These results imply that at least in the settings where specialised services are readily available, survival may no longer be the most relevant outcome, or the best criterion, for evaluating the impact of prenatal diagnosis on the outcome of CHD. The beneficial effects of prenatal diagnosis may be better sought by looking at more 'subtle' or long-term neurodevelopmental outcomes.

Strengths and limitations of this study

- ► We used data from a large, population-based, prospective cohort study to look at the association between prenatal diagnosis and the risk of infant (<1 year) mortality for newborns with four major congenital heart defects (CHDs): functionally univentricular heart, d-transposition of great arteries, tetralogy of Fallot and coarctation of aorta.
- ► We looked at both specific effects that may be associated with the four CHDs in our study, as well as, the overall effect. We included a test of homogeneity to assess whether there were significant differences in the relation between prenatal diagnosis and risk of infant mortality for the four CHDs.
- ► We did not evaluate the effects of prenatal diagnosis on pathways of care or on outcomes other than mortality.
- ► While data were from a large, population-based prospective cohort study, the number of cases for individual CHDs may not have been adequate to detect relatively small changes associated with prenatal diagnosis for individual CHDs.
- ► The extent to which our results may be generalisable to other regions in France, in particular rural areas where availability of high quality, specialist services is less than those in Paris, is difficult to know. The question of generalisability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

INTRODUCTION

Congenital heart defects (CHDs) are the most frequent group of congenital anomalies.[1] In addition to their relatively high prevalence (~1% of all births), CHDs also represent an important group of anomalies in that they are in many cases treatable. Nevertheless, and despite considerable progress in medical and surgical management of CHDs over the past three decades, CHDs remain a major cause of mortality and morbidity of perinatal origin and the first cause of infant death by malformation.[1–4]

Prenatal diagnosis and optimal post-natal management can result in secondary

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prevention of mortality and morbidity and improved long-term outcomes of newborns with CHD.[5–9] Indeed, previous studies have found that prenatal diagnosis can improve the chances of survival for newborns with certain types of CHD; this has been particularly the case for the transposition of great arteries (d-TGA) where studies in France as well as in the USA and the UK have found a higher survival for newborns with a prenatal diagnosis of their CHD. For other, very severe CHDs, including hypoplastic left heart syndrome, the results have not been consistent;[6 10–15] whereas some studies have found a survival advantage associated with prenatal diagnosis, others have not found this to be the case.

Limited population-based data are available on the CHD in general and on the association between prenatal diagnosis and mortality in particular.[6 14 16] Indeed, by far most of the existing literature is based on studies in specialised centres. This paucity of population-based data in turn complicates the interpretation of the existing literature as outcomes from specialised centres may not reflect those in the population of patients as a whole and be subject to transfer and/or survival bias. In addition, the mortality outcomes assessed are often limited to short-term, postsurgical mortality whereas longer-term mortality such as the overall infant (up to 1 year) mortality has been assessed much less frequently.

Using data from a large, prospective, population-based cohort (EPIdémiologie des CARDiopathies congénitales (EPICARD)) study, we assessed the probability of prenatal diagnosis and the impact of prenatal diagnosis on the risk of infant (until 1 year of age) mortality for newborns with four major CHDs, the tetralogy of Fallot (TOF), the coarctation of aorta (CoA), d-TGA and functionally univentricular heart (FUH).

MATERIALS AND METHODS

Data source

We used data from the EPICARD Study, which is a population-based, prospective cohort study with long-term follow-up of all children with a CHD born to women in the Greater Paris area (Paris and its surrounding suburbs). All cases (live births, terminations of pregnancy for fetal anomaly (TOPFA), fetal deaths) diagnosed in the prenatal period or up to 1 year of age in the birth cohorts between 1 May 2005 and 30 April 2008 born to women residing in Greater Paris were eligible for inclusion. Diagnoses were confirmed in specialised paediatric cardiology departments and for the majority of TOPFA and fetal deaths by a standardised pathology examination. When a pathology exam could not be done the diagnoses were confirmed by a paediatric cardiologist (LH) and a specialist in echocardiography (J-MJ) in the EPICARD Study group, using the results of prenatal echocardiography examination.

Multiple sources of data including all maternity units, paediatric cardiology and cardiac surgery centres, fetal and neonatal pathology departments, neonatal and paediatric intensive units, infant units and outpatient clinics in Greater Paris and a neighbouring tertiary care centre were regularly consulted to attain completeness of case registrations. Informed consent was obtained from study participants. The last cases included in the study were those in the 2008 birth cohort who were diagnosed in 2009. Follow-up of children in the EPICARD cohort is now completed and included assessment of children's health and neurodevelopmental outcomes until 8 years of age.

Details of coding and classification of cases for the EPICARD Study are given elsewhere.[17] Briefly, two paediatric cardiologists in the EPICARD Study group (LH, DB) attributed by consensus to each case, one, or in less than 20% of cases, two or up to six, six-digit code(s) of the long list of the International Paediatric and Congenital Cardiac Code.[18]

In order to identify 'isolated' cases of each of the four CHDs, we first excluded all cases that were associated with chromosomal anomalies and/or anomalies of other systems, including syndromes (see figure 1). In addition, when two or more of the four specific CHDs were present for the same fetus, we used the following hierarchical decision rule to classify the fetus as one and only one of the four CHDs in the study. The hierarchical order was as follows: FUH, d-TGA, TOF and CoA. Hence, fetuses in the study population with an FUH were classified as FUH regardless of any other associated anomalies. Those with TGA were classified as TGA except when FUH was also present. Those with TOF were classified as such (no other of the specific CHDs were present). Finally, fetuses with CoA were classified as such when none of the other three CHDs was also present.

Study population

Figure 1 shows the flow diagram for the selection of our study population. Overall, after excluding cases associated with chromosomal or other non-cardiac anomalies, including syndromes, our study population comprised 354 cases (live births, fetal deaths and terminations of pregnancy for fetal anomaly (TOPFA)), including 60 cases of tetralogy of Fallot (TOF), 77 coarctation of aorta (CoA), 85 TGA and 132 FUH.

Statistical analysis

For each of the four CHD, congenital heart defect (CHDs), we calculated the proportion of cases with a prenatal diagnosis, TOPFA and infant mortality with 95% binomial exact CIs. We conducted a Mantel-Haenszel analysis to test the association between prenatal diagnosis and probability of mortality and tested whether the association of prenatal diagnosis with mortality varied across the four CHDs by the test of homogeneity of risk ratios.

RESULTS

Table 1 shows the probability of prenatal diagnosis and TOFA for the four CHDs. Approximately, 95% of FUH (95% CI 89.4 to 97.8), 71% of TGA (95% CI 59.7 to 80.0),

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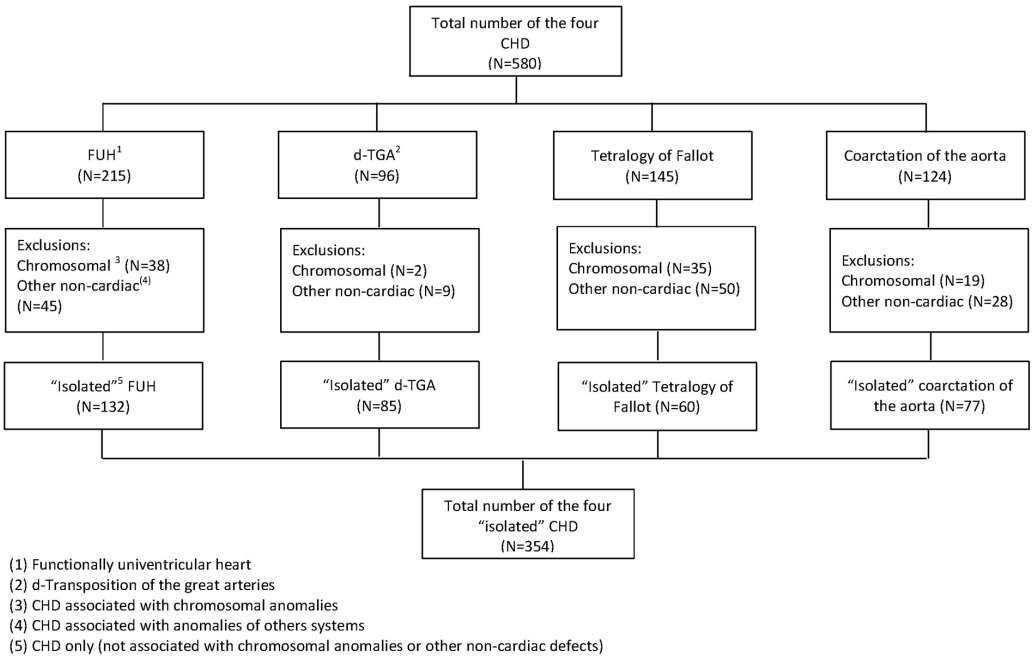

Figure 1 Flow chart for the study population.

68% of TOF (95% CI 55.0 to 79.7) and 43% of CoA (95% CI 31.6 to 54.6) were prenatally diagnosed (table 1). *Among the prenatally diagnosed cases* of FUH, about 70% (95% CI 61.6 to 78.2) had a TOPFA; this proportion was approximately 3% for TGA, 12% for TOF and 9% for CoA (table 1).

Table 2 shows the outcomes of pregnancy for the four specific CHDs *among all fetuses*. Live births accounted for more than 90% of TGA, TOF and CoA, whereas less than a third of FUH were born alive. TOPFA comprised 67% of all fetuses with FUH, 2% of fetuses with TGA, 8% of those with TOF and 4% of cases with FUH. Stillbirths accounted for about 4% of FUH and 2% of TGA, TOF and CoA.

Table 3 shows the relation between infant mortality and prenatal diagnosis for the four CHDs. Overall, we found no statistical evidence of a lower risk of mortality for cases that were prenatally diagnosed (Mantel-Haenszel combined risk ratio 1.1, 95% CI 0.5 to 2.2). The risk ratios of an infant death for prenatally diagnosed versus postnatally diagnosed cases were: 1.2 (95% CI 0.5 to 3.1) for FUH, 2.1 (95% CI 0.3 to 17.1) for TGA, 0.3 (95% CI 0.02 to 2.6) for TOF and 1.0 (95% CI 0.2 to 5.7) for CoA. We found no statistically significant differences in the association between the risk of mortality and prenatal diagnosis across the four CHDs (test of homogeneity of risk ratios, p=0.6).

DISCUSSION

Using prospective, population-based cohort data on 354 newborns with CHD, including FUH, d-TGA, TOF and CoA, we found that a considerable proportion of all cases were prenatally diagnosed. FUH, which can be diagnosed with the routine four-chamber view, had the highest probability of prenatal diagnosis (~95%) whereas those that need visualisation of the arterial trunks had a lower probability of prenatal diagnosis, particularly in the case of CoA (~50%) whereas for TGA and TOF more than two-thirds of the cases had a prenatal diagnosis.

Looking at the association between timing of (prenatal vs postnatal) diagnosis of CHD and risk of infant mortality, we did not find a statistically significant survival advantage associated with prenatal diagnosis for the four

Table 1 Prenatal diagnosis for four specific congenital heart defects (CHDs), EPIdémiologie des CARDiopathies congénitales (EPICARD) Population-Based Cohort Study

	Prenatal diagnosis*			% TOPFA†	
CHD	n	%	95% CI	%	95% CI
Functionally univentricular heart*	132	94.7	89.4 to 97.8	70.4	61.6 to 78.2
d-Transposition of the great arteries*	85	70.6	59.7 to 80.0	3.3	0.4 to 11.5
Tetralogy of Fallot*	60	68.3	55.0 to 79.7	12.2	4.1 to 26.2
Coarctation of the aorta*	77	42.9	31.6 to 54.6	9.1	1.9 to 24.3

*Cases with the specific International Paediatric and Congenital Cardiac Code for the given CHD, whether or not other CHD codes were also included; all cases with chromosomal or others anomalies were excluded.
†Terminations of pregnancy for fetal anomaly (TOPFA) among prenatally diagnoses cases.

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Table 2 Pregnancy outcomes for four specific congenital heart defects (CHDs), EPIdémiologie des CARDiopathies congénitales (EPICARD) population-based cohort study

		Live births		TOPFA*		Stillbirths	
CHD	N	%	95% CI	%	95% CI	%	95% CI
Functionally univentricular heart†	132	29.5	21.9 to 38.1	66.7	57.9 –to 74.6	3.8	1.2 to 8.6
d-Transposition of the great arteries†	85	95.2	88.4 –to 98.7	2.4	0.3 to 8.2	2.4	0.3 to 8.2
Tetralogy of Fallot†	60	90.0	79.5 to 96.2	8.3	2.8 to 18.4	1.7	0.04 to 8.9
Coarctation of the aorta†	77	94.8	87.2to 98.6	3.9	0.8 to 11.0	1.3	0.03 to 7.0

*Terminations of pregnancy for fetal anomaly (TOPFA) among the overall number of cases (ie, number of TOPFA divided by the total number of cases).
†Cases with the specific International Paediatric and Congenital Cardiac Code for the given CHD, whether or not other CHD codes were also included, all cases with chromosomal or others anomalies were excluded.

CHDs examined. Notwithstanding the limitations of the study and the caveats noted below, our findings suggest that in the current era, the beneficial effects of prenatal diagnosis in optimising prenatal and postnatal care of the newborns may be manifested, and hence should be looked for, in more 'subtle' or long-term outcomes, particularly those related to specific neurodevelopmental outcomes of the newborns with CHD.[19 20]

Our study has certain limitations. Despite the large size of our population-based cohort, the number of deaths for TGA, TOF and CoA was relatively small reflecting the high survival rates of newborns with these three CHDs. Therefore, the CIs for our risk ratio estimates for the relation between prenatal diagnosis and risk of mortality for each CHD were relatively wide and hence we may have missed an effect associated with prenatal diagnosis due to limited precision of estimates. This may have been particularly the case for TOF where the point estimate for the risk ratio suggested a lower risk of mortality for cases that were prenatally diagnosed but that this difference was not statistically significant. For the other three CHDs, the corresponding risk ratios were close to or higher than the null value. This suggests in turn that at least for FUH, TGA and CoA, the lack of a statistically significant association between prenatal diagnosis and risk of mortality may reflect the absence of relation between prenatal diagnosis and mortality. This may be due to the fact that with the improvements in postnatal care, the risk of mortality is nowadays low for these 'curable' CHDs (TOF, TGA and CoA) regardless of the timing of diagnosis. In the case of FUH, there remains a high risk of infant mortality whether or not the cases were prenatally diagnosed.

However, in addition to a relatively small sample size for individual CHD which may have resulted in lack of statistically significant results, an important caveat should be considered in interpreting our results on the relation between prenatal diagnosis and risk of mortality. It is at least possible that even in the case of an individual, well characterised defect, those that are prenatally diagnosed may be more severe than those diagnosed later. Hence, finding a survival advantage in relation to prenatal diagnosis, as has been found to be the case particularly for TGA in previous studies, may represent the 'lower limit' of the advantage that may be attributed to prenatal diagnosis, which can lead to a more optimal postnatal clinical and surgical management of CHD. Along the same lines,

Table 3 Association between prenatal diagnosis and risk of infant mortality for four specific congenital heart defects (CHDs), EPIdémiologie des CARDiopathies congénitales (EPICARD) Population-Based Cohort Study

	Prenatal diagnosis		Infant mortality				
CHD		n*	n†	%	95% CI	Risk ratio	95% CI
Functionally univentricular heart‡	No	7	3	42.9	9.9 to 81.6		
	Yes	32	17	53.1	34.7 to 70.9	1.2	0.5 to 3.1
d-Transposition of the great arteries‡	No	24	1	4.2	0.1 to 21.1		
	Yes	57	5	8.8	2.9 to 19.3	2.1	0.3 to 17.1
Tetralogy of Fallot‡	No	18	2	11.1	1.4 to 34.7		
	Yes	36	1	2.8	0.07 to 14.5	0.3	0.02 to 2.6
Coarctation of the aorta‡	No	44	3	6.8	1.4 to 18.7		
	Yes	29	2	6.9	0.8 to 22.8	1.0	0.2 to 5.7

*N = number of live births (denominator data).
†n= number of deaths (numerator data).
‡Cases with the specific International Paediatric and Congenital Cardiac Code for the given CHD; whether or not other CHD codes were also included, all cases with chromosomal or others anomalies were excluded.

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lack of a survival advantage, may be due to an adverse selection bias for cases diagnosed prenatally. This 'negative' finding can hence be misleading as the absence of an effect associated with prenatal diagnosis, would actually indicate that prenatal diagnosis improves survival.

We also conducted an exploratory analysis (detailed results available from authors) to look at the possible effects of cardiac anomalies that may have been associated with the four CHDs in our study.

Specifically, we looked separately at each of the four CHDs when they were completely isolated, that is, when there were no cardiac anomalies present other than the four CHDs themselves versus when they were associated with other cardiac defects (note that cases with non-cardiac defects, including syndromes as well as chromosomal anomalies had already been excluded).

In general, when the defect was completely isolated the risk of mortality was lower than when the defect was associated with other cardiac anomalies. However, the relation between prenatal diagnosis and risk of mortality was not appreciably different for the completely isolated cases versus those associated with other cardiac anomalies. It should be noted that this stratified analysis can at best be considered exploratory as the number of events (deaths) in each group were quite small.

Nevertheless, the results of this analysis make clinical sense. Even though we did not look specifically at postoperative mortality, associated cardiac anomalies can in particular render the surgical interventions more complex, which can in turn explain at least some of the higher risks of mortality in the group of defects associated with other cardiac anomalies.

Our findings reflect population-based data from the Greater Paris area. In our region, the organisation of prenatal diagnostic services is well codified and includes in particular the constitution of 48 multidisciplinary centres for prenatal diagnosis across the country, including 4 in Paris and 5 in its surrounding suburbs. By law, the severity of the fetal anomaly must be certified by two experts from these centres in order for TOPFA to be authorised. For cases in which either TOPFA is not an appropriate decision ('curable' or not sufficiently severe anomalies) or for which women opt to continue their pregnancy even if the experts consider that TOPFA is an acceptable option, the centres play an important role in the perinatal management of cases to optimise care for both mothers and their affected newborns. Mandates for the exclusive coordination of prenatal diagnosis services by these multidisciplinary centres are likely to have contributed to a wider availability of high-quality prenatal diagnostic services in our population. Moreover, there is a high concentration of specialised services for postnatal care of newborns with CHD, including Neonatal Intensive Care Units (NICUs), Paediatric Intensive Care Units (PICUs) and cardiac surgery centres. This, in turn, has the effect that the time required for transfers (due to relative geographical proximity) is generally not very long even if we did not specifically address this question in our study. Hence, even cases with postnatal diagnosis can usually be transferred to tertiary, specialised centres for optimal care. Therefore, the effect of prenatal diagnosis may be relatively lower in our population versus one in say urban areas or in general when one or only a few tertiary centres are available for transfer of patients with CHD. Finally, it is worth noting that, at least for the time being, routine pulse oximetry is not practised in France. There is, however, an ongoing study in the Aquitaine area for looking at the impact of pulse oximetry for newborns with CHD.

Given these considerations, the extent to which our results may be generalisable to other regions in France, in particular rural areas where availability of high quality, specialist services is less than those in Paris, is difficult to know. The question of generalisability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

We should emphasise that interpreting these results as proof for a general lack of efficacy of prenatal diagnosis for optimal management and outcomes of CHD would clearly be misguided and misleading. Instead, our results imply that survival may no longer be the most relevant outcome, or the best criterion, for evaluating the impact of prenatal diagnosis on outcomes of CHD. Indeed, as recent studies have shown, prenatal diagnosis can improve the neurodevelopmental outcomes of newborns with CHD, for example, in case of TGA.[19–22] What is needed now is to assess whether these results that are based on hospital-based studies from specialised centres also hold at the population level and for other CHDs. It would also be worthwhile to see whether prenatal diagnosis may continue to be associated with better survival outcomes in settings where specialised services are not readily available and require in utero or early transfer of newborns to distant referral centres. Moreover, the underlying clinical and pathophysiological mechanisms that may explain the beneficial effects of prenatal diagnosis on outcomes of newborns with CHD require further study.[23]

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Contributors FG and BK are the principal investigators of this study, had full access to the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. BK and FG conceived the study. NL and BK conducted the statistical analysis with the assistance of MB and in consultation with FG. LH, DB and J-MJ provided clinical expertise. BK wrote the first draft of the article. All coauthors made substantial contributions to the interpretation of results and revisions of the manuscript.

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