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Impact of prenatal diagnosis on survival of newborns with four congenital heart defects: Population-based cohort study

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Abstract

Objectives: 1) Assess the population-level probability of prenatal diagnosis and termination of pregnancy for foetal anomaly for four major congenital heart defects; 2) Examine, using population-based data, the relation between timing of (pre- vs. post-natal) diagnosis and risk of infant (i.e., < 1-year) mortality for four major CHD. A secondary objective was

Design: Population-based cohort (the EPICARD) study

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

Patients: 354 cases of four major CHD, 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 (pre vs. post-natal) 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 CHD was not statistically significant.

Conclusion: These results imply that at least in the settings where specialized 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 neuro-developmental outcomes.

Strengths and limitations of this study

Strengths

- 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 CHD: 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 CHD 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 CHD.

Limitations

- 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 CHD may not have been adequate to detect relatively small changes associated with prenatal diagnosis for individual CHD.

- The extent to which our results may be generalizable 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 generalizability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

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Introduction

Congenital heart defects (CHD) are the most frequent group of congenital anomalies[1]. In addition to their relatively high prevalence (~ 1% of all births), CHD 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 CHD over the past three decades, CHD 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 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 (TGA) where studies in France as well as in the United States and the United Kingdom have found a higher survival for newborns with a prenatal diagnosis of their CHD. For other, very severe CHD, 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 specialized centres. This paucity of population-based data in turn complicates the interpretation of the existing literature as outcomes from specialized 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, post-surgical mortality whereas longer term mortality such as the overall infant (up to one-year) mortality has been assessed much less frequently.

Using data from a large, prospective, population-based cohort (EPICARD) study, we assessed the probability of prenatal diagnosis and the impact of prenatal diagnosis on the risk of infant (until one year of age) mortality for newborns with four major CHD, the Tetralogy of Fallot (TOF), the Coarctation of Aorta (CoA), the Transposition of Great Arteries (d-TGA) and Functionally Univentricular Heart (FUH).

Materials and Methods

Data source

We used data from the EPICARD (EPIdémiologie des CARDiopathies congénitales) 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, TOPFA, foetal deaths) diagnosed in the prenatal period or up to one year of age in the birth cohorts between May 1st 2005 and April 30th 2008 born to women residing in Greater Paris were eligible for inclusion. Diagnoses were confirmed in specialized paediatric cardiology departments and for the majority of TOPFA and foetal deaths by a standardized pathology examination. When a pathology exam could not be done the diagnoses were confirmed by a paediatric cardiologist (LH) and a specialist in echocardiography (JMJ) 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, foetal 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 and the study was approved by an ethics committee (French National Committee of Information and Liberty). 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 neuro-developmental outcomes until eight 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 (IPCCC)[18].

When two or more of the four specific CHD were present for the same foetus, we used the following hierarchical decision rule to classify the foetus as one and only one of the four CHD in the study. The hierarchical order was as follows: FUH, TGA, TOF and CoA. Hence, foetuses in the study population with a 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 CHD were present). Finally, foetuses with CoA were classified as such when none of the other three CHD was also present.

Study population

After excluding cases associated with chromosomal or other anomalies, our study population comprised 354 cases (live births, foetal deaths and TOPFA), including 60 cases of TOF, 77 CoA, 85 TGV and 132 FUH.

Statistical analysis

For each of the four CHD, we calculated the proportion of cases with a prenatal diagnosis, terminations of pregnancy for foetal anomaly (TOPFA) and infant mortality with 95% binomial exact confidence intervals. 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 CHD by the test of homogeneity of risk ratios.

Results

Table 1 shows the probability of prenatal diagnosis and TOFA for the four CHD. Approximately, 95% of FUH (95% CI, 89.4 – 97.8), 71% of TGA (95% CI, 59.7 – 80.0), 68% of TOF (95% CI, 55.0 – 79.7) and

43% of CoA (95% CI, 31.6 – 54.6) were prenatally diagnosed (Table 1). *Among the prenatally diagnosed cases* of FUH, about 70% (95% CI, 61.6 – 78.2) had a termination of pregnancy for foetal anomaly (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 CHD *among all foetuses*. Live births accounted for more than 90% of TGA, TOF and CoA, whereas less than one-third of FUH were born alive. TOPFA comprised 67% of all foetuses with FUH, 2% of foetuses 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 CHD. 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 – 2.2). The risk ratios of an infant death for prenatally diagnosed vs. postnatally diagnosed cases were: 1.2 (95% CI, 0.5 – 3.1) for FUH, 2.1 (95% CI, 0.3 – 17.1) for TGA, 0.3 (0.02 – 2.6) for TOF and 1.0 (95% CI, 0.2 – 5.7) for CoA. We found no statistically significant differences in the association between the risk of mortality and prenatal diagnosis across the four CHD (Test of homogeneity of risk ratios, p = 0.6).

Discussion

Using prospective, population-based cohort data on 354 newborns with CHD, including Functionally Univentricular Heart, Transposition of Great Arteries, Tetralogy of Fallot and Coarctation of the aorta, 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 visualization 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 (pre- vs post-natal) diagnosis of CHD and risk of infant mortality, we did not find a statistically significant survival advantage associated with prenatal diagnosis for the four CHD examined. This finding suggests that in the current era, the beneficial effects of prenatal diagnosis in optimizing pre- and post-natal 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 neuro-developmental outcomes of the newborns with CHD[19;20].

Our study has certain limits. 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 CHD. Therefore, the confidence intervals 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 CHD, 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 the timing of diagnosis and risk of mortality in our data may in fact reflect the absence of relation between prenatal diagnosis and mortality. This may be due to the fact that with the improvements in post-natal care, the risk of mortality is nowadays low for

these “curable” CHD (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.

Our study was based on population-based data from the Greater Paris area. In our region, the organization of prenatal diagnostic services is well-codified and includes in particular the constitution of 48 Multi-disciplinary Centres for Prenatal Diagnosis across the country, including four in Paris and five in its surrounding suburbs. By law, the severity of the foetal anomaly must be certified by two experts from these centres in order for the TOPFA to be authorized. 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 optimize care for both mothers and their affected newborns. Mandates for the exclusive coordination of prenatal diagnosis services by these multi-disciplinary 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 specialized services for postnatal care of newborns with CHD, including NICUs, PICUs and cardiac surgery centres.

Hence, the extent to which our results may be generalizable 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 generalizability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

We should emphasize 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 neuro-developmental outcomes of newborns with CHD, for example in case of the TGA[19-22]. What is needed now is to assess whether

these results that are based on hospital-based studies from specialized centres also hold at the population-level and for other CHD. It would also be worthwhile to see whether prenatal diagnosis may continue to be associated with better survival outcomes in settings where specialized 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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Acknowledgements and Disclosure section

B Khoshnood and N Lelong had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest:

The authors have no conflicts of interest to declare. The funding sources had no role in the study design, data collection, data interpretation, or the writing of the manuscript.

Contributors:

B. Khoshnood and F. Goffinet conceived the study. N. Lelong and B. Khoshnood with help from Morgane Ballon conducted the statistical analysis with the assistance of Morgane Ballon and in consultation with F. Goffinet. L. Houyel, D. Bonnet and JM Jouannic provided clinical expertise. B. Khoshnood wrote the first draft of the article. All co-authors made substantial contributions to the interpretation of results and revisions of the manuscript.

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Table 1 : Prenatal diagnosis for four specific CHD, EPICARD population-based cohort study

Congenital Heart Defect	Prenatal Diagnosis[1]			% TOPFA[2]	
	N	%	95% CI	%	95% CI
Functionally Univentricular Heart[1]	132	94.7	89.4-97.8	70.4	61.6-78.2
d-Transposition of the great arteries[1]	85	70.6	59.7-80.0	3.3	0.4-11.5
Tetralogy of Fallot[1]	60	68.3	55.0-79.7	12.2	4.1-26.2
Coarctation of the aorta[1]	77	42.9	31.6-54.6	9.1	1.9-24.3

(1) Cases with the specific IPCCC code for the given CHD, whether or not other CHD codes were also included; all cases with chromosomal or others anomalies were excluded

(2) Terminations of Pregnancy for Fetal Anomaly (TOPFA) among prenatally diagnoses cases

Table 2 : Pregnancy outcomes for four specific CHD, EPICARD population-based cohort study

Congenital Heart Defect	Live births			TOPFA[2]		Stillbirths	
	N	%	95% CI	%	95% CI	%	95% CI
Functionally univentricular heart[1]	132	29.5	21.9-38.1	66.7	57.9-74.6	3.8	1.2-8.6
d-Transposition of the great arteries[1]	85	95.2	88.4-98.7	2.4	0.3-8.2	2.4	0.3-8.2
Tetralogy of Fallot[1]	60	90.0	79.5-96.2	8.3	2.8-18.4	1.7	0.04-8.9
Coarctation of the aorta[1]	77	94.8	87.2-98.6	3.9	0.8-11.0	1.3	0.03-7.0

(1) Cases with the specific IPCCC code for the given CHD, whether or not other CHD codes were also included; all cases with chromosomal or others anomalies were excluded

(2) Terminations of Pregnancy for Fetal Anomaly (TOPFA) among the overall number of cases (i.e number of TOPFA divided by the total number of cases)

Table 3 : Association between prenatal diagnosis and risk of infant mortality for four specific CHD, EPICARD population-based cohort study

Congenital Heart Defect	Prenatal Diagnosis	Infant mortality				
		N	%	95% CI	Risk Ratio	95% CI
Functionally univentricular heart[(1)]	No	7	42.9	9.9-81.6		
	Yes	32	53.1	34.7-70.9	1.2	0.5 - 3.1
d-Transposition of the great arteries[(1)]	No	24	4.2	0.1-21.1		
	Yes	57	8.8	2.9-19.3	2.1	0.3 - 17.1
Tetralogy of Fallot[(1)]	No	18	11.1	1.4-34.7		
	Yes	36	2.8	0.07-14.5	0.3	0.02-2.6
Coarctation of the aorta[(1)]	No	44	6.8	1.4-18.7		
	Yes	29	6.9	0.8-22.8	1.0	0.2-5.7

(1) Cases with the specific IPCCC 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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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 foetal anomaly for four major congenital heart defects; 2) Examine, using population-based data, the relation between timing of (pre- vs. post-natal) diagnosis and risk of infant (i.e., < 1-year) mortality for four major CHD.

Design: Population-based cohort (the EPICARD) study

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

Patients: 354 cases of four major CHD, 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 (pre vs. post-natal) 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 CHD was not statistically significant.

Conclusion: These results imply that at least in the settings where specialized 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 neuro-developmental outcomes.

Strengths and limitations of this study

Strengths

- 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 CHD: 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 CHD 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 CHD.

Limitations

- 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 CHD may not have been adequate to detect relatively small changes associated with prenatal diagnosis for individual CHD.

- The extent to which our results may be generalizable 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 generalizability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

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Introduction

Congenital heart defects (CHD) are the most frequent group of congenital anomalies[1]. In addition to their relatively high prevalence (~ 1% of all births), CHD 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 CHD over the past three decades, CHD 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 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 (TGA) where studies in France as well as in the United States and the United Kingdom have found a higher survival for newborns with a prenatal diagnosis of their CHD. For other, very severe CHD, 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 specialized centres. This paucity of population-based data in turn complicates the interpretation of the existing literature as outcomes from specialized 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, post-surgical mortality whereas longer term mortality such as the overall infant (up to one-year) mortality has been assessed much less frequently.

Using data from a large, prospective, population-based cohort (EPICARD) study, we assessed the probability of prenatal diagnosis and the impact of prenatal diagnosis on the risk of infant (until one year of age) mortality for newborns with four major CHD, the Tetralogy of Fallot (TOF), the Coarctation of Aorta (CoA), the Transposition of Great Arteries (d-TGA) and Functionally Univentricular Heart (FUH).

Materials and Methods

Data source

We used data from the EPICARD (EPIdémiologie des CARDiopathies congénitales) 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, TOPFA, foetal deaths) diagnosed in the prenatal period or up to one year of age in the birth cohorts between May 1st 2005 and April 30th 2008 born to women residing in Greater Paris were eligible for inclusion. Diagnoses were confirmed in specialized paediatric cardiology departments and for the majority of TOPFA and foetal deaths by a standardized pathology examination. When a pathology exam could not be done the diagnoses were confirmed by a paediatric cardiologist (LH) and a specialist in echocardiography (JMJ) 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, foetal 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 and the study was approved by an ethics committee (French National Committee of Information and Liberty). 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 neuro-developmental outcomes until eight 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 (IPCCC)[18].

In order to identify "isolated" cases of each of the four CHD, 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 CHD were present for the same foetus, we used the following hierarchical decision rule to classify the foetus as one and only one of the four CHD in the study. The hierarchical order was as follows: FUH, TGA, TOF and CoA. Hence, foetuses in the study population with a 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 CHD were present). Finally, foetuses with CoA were classified as such when none of the other three CHD 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, foetal deaths and TOPFA), including 60 cases of TOF, 77 CoA, 85 TGV and 132 FUH.

Statistical analysis

For each of the four CHD, we calculated the proportion of cases with a prenatal diagnosis, terminations of pregnancy for foetal anomaly (TOPFA) and infant mortality with 95% binomial exact confidence intervals. 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 CHD by the test of homogeneity of risk ratios.

Results

Table 1 shows the probability of prenatal diagnosis and TOFA for the four CHD. Approximately, 95% of FUH (95% CI, 89.4 – 97.8), 71% of TGA (95% CI, 59.7 – 80.0), 68% of TOF (95% CI, 55.0 – 79.7) and 43% of CoA (95% CI, 31.6 – 54.6) were prenatally diagnosed (Table 1). *Among the prenatally diagnosed cases* of FUH, about 70% (95% CI, 61.6 – 78.2) had a termination of pregnancy for foetal anomaly (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 CHD *among all foetuses*. Live births accounted for more than 90% of TGA, TOF and CoA, whereas less than one-third of FUH were born alive. TOPFA comprised 67% of all foetuses with FUH, 2% of foetuses 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 CHD. 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 – 2.2). The risk ratios of an infant death for prenatally diagnosed vs. postnatally diagnosed cases were: 1.2 (95% CI, 0.5 – 3.1) for FUH, 2.1 (95% CI, 0.3 – 17.1) for TGA, 0.3 (0.02 – 2.6) for TOF and 1.0 (95% CI, 0.2 – 5.7) for CoA. We found no statistically significant differences in the association between the risk of mortality and prenatal diagnosis across the four CHD (Test of homogeneity of risk ratios, p = 0.6).

Discussion

Using prospective, population-based cohort data on 354 newborns with CHD, including Functionally Univentricular Heart, Transposition of Great Arteries, Tetralogy of Fallot and Coarctation of the aorta, 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 visualization 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 (pre- vs post-natal) diagnosis of CHD and risk of infant mortality, we did not find a statistically significant survival advantage associated with prenatal diagnosis for the four CHD 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 optimizing pre- and post-natal 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 neuro-developmental outcomes of the newborns with CHD[19;20].

Our study has certain limits. 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 CHD. Therefore, the confidence intervals 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 CHD, 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 post-natal care, the risk of mortality is nowadays low for these "curable" CHD (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 post-natal clinical and surgical management of CHD. Along the same lines, 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 CHD in our study. Specifically, we looked separately at each of the four CHD when they were completely isolated, i.e., when there were no cardiac anomalies present other than the four CHD themselves vs. 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 vs. 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 post-operative mortality, associated cardiac anomalies can in particular render the surgical interventions more complex, which can in turn explain at least some of the higher risk 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 organization of prenatal diagnostic services is well-codified and includes in particular the constitution of 48 Multi-disciplinary Centres for Prenatal Diagnosis across the country, including four in Paris and five in its surrounding suburbs. By law, the severity of the foetal anomaly must be certified by two experts from these centres in order for the TOPFA to be authorized. 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 optimize care for both mothers and their affected newborns. Mandates for the exclusive coordination of prenatal diagnosis services by these multi-disciplinary 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 specialized services for postnatal care of newborns with CHD, including NICUs, 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 vs. 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 practiced 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 generalizable 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 generalizability of our results to other countries in Europe or elsewhere is also an open one and requires further study.

We should emphasize 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 neuro-developmental outcomes of newborns with CHD, for example in case of the TGA[19-22]. What is needed now is to assess whether these results that are based on hospital-based studies from specialized centres also hold at the population-level and for other CHD. It would also be worthwhile to see whether prenatal diagnosis may continue to be associated with better survival outcomes in settings where specialized 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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Acknowledgements and Disclosure section

B Khoshnood and N Lelong had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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B. Khoshnood and F. Goffinet conceived the study. N. Lelong and B. Khoshnood with help from Morgane Ballon conducted the statistical analysis with the assistance of Morgane Ballon and in consultation with F. Goffinet. L. Houyel, D. Bonnet and JM Jouannic provided clinical expertise. B. Khoshnood wrote the first draft of the article. All co-authors made substantial contributions to the interpretation of results and revisions of the manuscript.

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Table 1 : Prenatal diagnosis for four specific CHD, EPICARD population-based cohort study

Congenital Heart Defect	Prenatal Diagnosis[1]			% TOPFA[2]	
	N	%	95% CI	%	95% CI
Functionally Univentricular Heart[1]	132	94.7	89.4-97.8	70.4	61.6-78.2
d-Transposition of the great arteries[1]	85	70.6	59.7-80.0	3.3	0.4-11.5
Tetralogy of Fallot[1]	60	68.3	55.0-79.7	12.2	4.1-26.2
Coarctation of the aorta[1]	77	42.9	31.6-54.6	9.1	1.9-24.3

(1) Cases with the specific IPCCC code for the given CHD, whether or not other CHD codes were also included; all cases with chromosomal or others anomalies were excluded

(2) Terminations of Pregnancy for Foetal Anomaly (TOPFA) among prenatally diagnoses cases

Table 2 : Pregnancy outcomes for four specific CHD, EPICARD population-based cohort study

Congenital Heart Defect	Live births			TOPFA[2]		Stillbirths	
	N	%	95% CI	%	95% CI	%	95% CI
Functionally univentricular heart[1]	132	29.5	21.9-38.1	66.7	57.9-74.6	3.8	1.2-8.6
d-Transposition of the great arteries[1]	85	95.2	88.4-98.7	2.4	0.3-8.2	2.4	0.3-8.2
Tetralogy of Fallot[1]	60	90.0	79.5-96.2	8.3	2.8-18.4	1.7	0.04-8.9
Coarctation of the aorta[1]	77	94.8	87.2-98.6	3.9	0.8-11.0	1.3	0.03-7.0

(1) Cases with the specific IPCCC code for the given CHD, whether or not other CHD codes were also included;
all cases with chromosomal or others anomalies were excluded
(2) Terminations of Pregnancy for Fetal Anomaly (TOPFA) among the overall number of cases (i.e number of TOPFA divided by the total number of cases)

Table 3 : Association between prenatal diagnosis and risk of infant mortality for four specific CHD, EPICARD population-based cohort study

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

(1) Cases with the specific IPCCC code for the given CHD, whether or not other CHD codes were also included; all cases with chromosomal or others anomalies were excluded

#N = number of live births (denominator data)

✞n= number of deaths (numerator data)

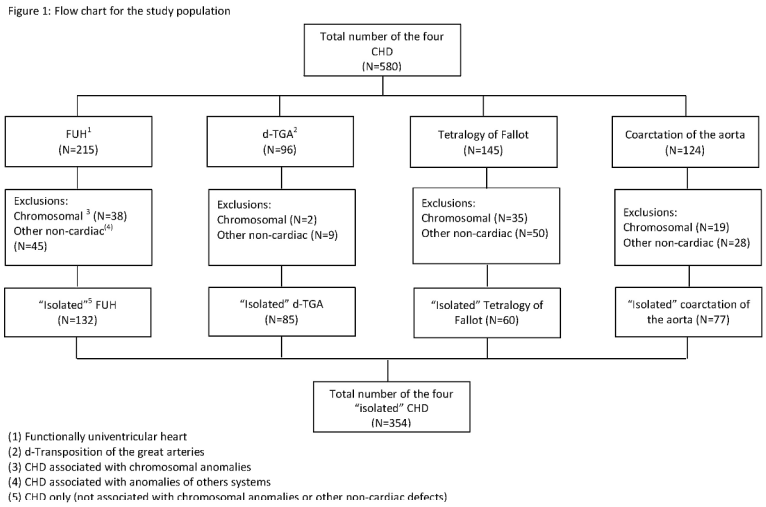

Figure 1. Flow chart for the study population

297x209mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract Pages 1 and 2 (population-based, prospective cohort study in France)	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale Page 5	2	Explain the scientific background and rationale for the investigation being reported
Objectives – Page 6.	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design – see Data source (pp. 7-8)	4	Present key elements of study design early in the paper
Setting – see Data source, p. 8	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants See Study Population (pp. 6-7) and Flow diagram, Figure 1, page 16	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Pages 7-8, including Statistical Analysis	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement Pages 7-8	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias Excluded cases associated with chromosomal anomalies / non-cardiac anomalies, including syndromes (p. 8) Acknowledged and discussed the possibility of variable severity for cases prenatally vs. postnatally diagnosed (Discussion, pp. 10-11)	9	Describe any efforts to address potential sources of bias
Study size p. 8 – study population	10	Explain how the study size was arrived at
Quantitative variables Our variables were categorical.	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods Page 8. Exploratory analysis described briefly in the Discussion (p. 11) for looking at the potential impact of cardiac anomalies associated with the four examined in our study (detailed results available from authors).	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was

No missing data for prenatal diagnosis or mortality. Exploratory analysis referred to above.		addressed (*g*) Describe any sensitivity analyses
Results		
Participants See Flow Diagram p. 16	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data Data on prenatal diagnosis, pregnancy outcomes (TOPFA, stillbirths and live births) provided on page 9 No missing data for the exposure (prenatal vs. postnatal diagnosis) or the main outcome (infant mortality)	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data p. 9	15*	Report numbers of outcome events or summary measures over time
Main results p.9 and Tables 1-3	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses Exploratory analysis referred to above	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results paragraphs 1-2, Discussion, pp. 9-10	18	Summarise key results with reference to study objectives
Limitations Discussion, pp.10-11	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation pp. 9-10, p. 13	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability p. 12	21	Discuss the generalisability (external validity) of the study results
Other information		
Page 16 (the funding sources had no role in the study design, data collection, data interpretation, or writing of the manuscript).	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.