## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Impact of prenatal diagnosis on survival of newborns with four congenital heart defects: A prospective, population-based cohort study in France (the EPICARD Study) |
| **AUTHORS** | Khoshnood, Babak; Lelong, Nathalie; Houyel, Lucile; Bonnet, Damien; Ballon, Morgane; Jouannic, Jean-Marie; Goffinet, François |

## VERSION 1 – REVIEW

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| **REVIEWER** | Diana Wellesley<br>Wessex Clinical Genetics Service<br>Princess Anne Hospital<br>Southampton SO16 5YA<br>UK |
| **REVIEW RETURNED** | 23-Jun-2017 |

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| **GENERAL COMMENTS** | A very interesting study using a superb cardiac database. The paper is well and logically written but I have a few questions and recommendations:<br><br>1. You have excluded cases with a chromosomal aetiology but do not specify whether each foetus / child had any non-cardiac anomalies as well. If only cases with isolated cardiac anomaly cases were selected perhaps you could specify this. If additional anomalies were accepted, perhaps these could be listed, or mentioned, as they could also affect mortality.<br><br>2. Presumably it is possible / likely that the prenatally detected cases were more severe than those not found before birth? Particularly the FUH cases where a 4 chamber view would be expected to be sought in all cases. Was this considered by the cardiologists when the cases were coded / stratified? Unless there is certainty that those detected prenatally were not more severe, this should be added to the limitations and discussion. It could be argued that if those prenatally detected were more severe, but their mortality was not greater, then they did do better thanks to the in utero diagnosis.<br><br>3. In TGA, the presence or absence of a VSD is relevant to the early survival of a baby, particularly those not prenatally diagnosed who are therefore unlikely to be provided with immediate, delivery room prostaglandin treatment. Can you please comment on this? The fact your mortality rate was not higher in those undiagnosed is impressive - is an oxygen saturation monitor used on all babies prior to discharge? If this is the case, it is worth stating. |

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| | 4. I find table 3 rather hard to understand. I presume you are providing the numbers of babies in each group that were live born and then giving a risk ratio of those that died? It would be much clearer if you could label the first column 'live born case numbers' or whatever it is, and then give the actual numbers of those who died for each group followed by the risk ratio.<br><br>Altogether a very useful paper with high quality data but these considerations, in my opinion, would add clarity. |

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| **REVIEWER** | Marian Bakker<br>University Medical Center Groningen<br>Groningen, The Netherlands |
| **REVIEW RETURNED** | 06-Jul-2017 |

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| **GENERAL COMMENTS** | This is an interesting paper on probablity of prenatal diagnosis and its effect of infant mortality in a population-based cohort of fetuses and neonates diagnosed with a severe CHD. The main limitation of the study is that numbers are low.<br>Abstract:<br>There is an unfinished sentence in the objectives of the abstract.<br><br>Introduction:<br>Why did the authors specifically choose to include these 4 heart defects?<br>It would be intersting to give some information on the prenatal screening policy in the study period in the Paris area, such as time of US and way of visualisation of the cardiac structures.<br><br>Methods:<br>After exclusion 354 cases remained. What was the initial study population, how many were excluded because of associated anomalies or no informed consent? What was the total corresponding prevalence of these four CHD types?<br><br>Results:<br>Please report also numbers in the tables, not just %. People will calculate back to numbers, at least I did. If numbers are less than 100, % should be reported without digits, also in the tables. Table 2 can be omitted, since the % are also reported in the tekst.<br>Table 3 is confusing in its layout. The numbers refer to number of LB cases per prenatal diagnosis category, the % to the first year mortality. There were 7 LB cases after PND, of which 3 died in the first year (43%).<br><br>Discussion:<br>Since the numbers are small, the CI intervals are wide and an decreased risk or even an increased risk of mortality in prenatally diagnosed compared to postnatally diagnosed cases can not be ruled out. For Fallot the point estimate suggests lower risk of 1st year mortality, for TGA the point estimate suggests higher risk of mortality for prenatally diagnosed cases (not close to te null as authors mentioned). Could it be that more severe cases of TGA are amenable for prenatal diagnosis, but also are at risk for infant mortality?<br>Were there any other factors that may be related to mortality, such as gestational age at birth and why did the authors did not take this information into account? |

**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**
Reviewer Name: Diana Wellesley
Institution and Country: Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton SO16 5YA, UK
Please state any competing interests: None declared

Please leave your comments for the authors below
"A very interesting study using a superb cardiac database. The paper is well and logically written but I have a few questions and recommendations:"
We thank our reviewer for these encouraging comments.

Comment 1. You have excluded cases with a chromosomal aetiology but do not specify whether each foetus / child had any non-cardiac anomalies as well. If only cases with isolated cardiac anomaly cases were selected perhaps you could specify this. If additional anomalies were accepted, perhaps these could be listed, or mentioned, as they could also affect mortality."

Response: We agree that this point needed clarification. By "isolated" defects, we meant that the cases analysed were those that were not associated with either chromosomal anomalies or with non-cardiac structural anomalies (including syndromes). We have made this more explicit in the revised version (p. 8 and Discussion, p. 11)

Comment 2. Presumably it is possible / likely that the prenatally detected cases were more severe than those not found before birth? Particularly the FUH cases where a 4 chamber view would be expected to be sought in all cases. Was this considered by the cardiologists when the cases were coded / stratified? Unless there is certainty that those detected prenatally were not more severe, this should be added to the limitations and discussion. It could be argued that if those prenatally detected were more severe, but their mortality was not greater, then they did do better thanks to the in utero diagnosis."

Response: We agree with our reviewer. Indeed, it is possible, perhaps probable, 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, as our reviewer has pointed out, lack of a survival advantage, may be due to an adverse selection bias for cases diagnosed prenatally. This "negative" finding can be misleading as the absence of an effect associated with prenatal diagnosis, would actually indicate that prenatal diagnosis improves survival.

Another point that should be considered regarding our main finding of the "absence" of a survival advantage related to prenatal diagnosis has to do with our study population. Specifically, as our study was based in Paris and its surrounding suburbs, 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.

We have added these points to the Discussion section (pp. 10-12 of the revised manuscript).

Comment 3. In TGA, the presence or absence of a VSD is relevant to the early survival of a baby, particularly those not prenatally diagnosed who are therefore unlikely to be provided with immediate, delivery room prostaglandin treatment. Can you please comment on this? The fact your mortality rate was not higher in those undiagnosed is impressive – is an oxygen saturation monitor used on all babies prior to discharge? If this is the case, it is worth stating."

Response: We agree that VSD in TGA may protect from early neonatal demise. In general, as our reviewer has pointed out, for all of the four CHD in our study, associated cardiac anomalies could modify the risk of mortality and also, at least theoretically, affect the relation between prenatal diagnosis and risk of mortality (analogous to an interaction effect).

To examine this question further empirically, we looked separately at each of the four CHD when they were "isolated", i.e., when there were not 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 were already excluded).
In general, when the defect was "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 "isolated" cases vs. those associated with other cardiac anomalies (detailed results available from authors).

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.
With regard to pulse oximetry, it is not (at least not yet) a routine practice in France. There is an ongoing study in the Aquitaine area for looking at the impact of pulse oximetry for newborns with CHD.

We have included these points in the Discussion section (pp. 11-12).

Comment 4. I find table 3 rather hard to understand. I presume you are providing the numbers of babies in each group that were live born and then giving a risk ratio of those that died? It would be much clearer if you could label the first column 'live born case numbers' or whatever it is, and then give the actual numbers of those who died for each group followed by the risk ratio."

Response: We have modified Table 3 as suggested by our reviewer.

"Altogether a very useful paper with high quality data but these considerations, in my opinion, would add clarity."

We are grateful to our reviewer for her important and thoughtful comments. We hope to have adequately addressed these omments in our reply and in the revised version of the manuscript.

**Reviewer: 2**
Reviewer Name: Marian Bakker
Institution and Country: University Medical Center Groningen,
Groningen, The Netherlands
Please state any competing interests: None declared

Please leave your comments for the authors below

Comment: ”This is an interesting paper on probablity of prenatal diagnosis and its effect of infant mortality in a population-based cohort of fetuses and neonates diagnosed with a severe CHD. The main limitation of the study is that numbers are low.”

Response: We thank our reviewer for these encouraging comments. We agree with the limitation mentioned even if the total number of cases was more than 300 (the largest prospective, population-based cohort of these four major CHD included in our study for looking at this question). For individual defects we had reasonable even if not very large numbers that would be difficult, if not impossible to come by in a prospective, population-based cohort design as was the case for our study.

We have acknowledged this limitation (relatively small number of events) in our study in the Discussion section (p. 10)

Abstract:
Comment: “There is an unfinished sentence in the objectives of the abstract.”

Response: Thank you for pointing this out. We meant to delete this sentence and we have done so completely now.

Introduction:
Comment: “Why did the authors specifically choose to include these 4 heart defects?”

Response: We selected these four defects as they represent four major CHD in terms of their prevalence. Moreover, the diagnosis of these four defects represents different modalities for prenatal diagnosis, with FUH being easily diagnosed prenatally with a routine, four-chamber view whereas the other defects require more specialized ultrasound examinations for confirmation of diagnosis. Another reason for looking at these major defects was that previous studies have found inconsistent effects associated with prenatal diagnosis for these defects. In particular, some studies have found prenatal diagnosis to confer a survival advantage for hypoplastic left heart syndrome whereas others have not found such a survival advantage. In contrast, for TGA, both large hospital-based and population-based studies have consistently found a survival advantage related to prenatal diagnosis (Bonnet, Circulation 1999, Khoshnood, Pediatrics 2005, Blyth, BJOG 2008).

“It would be interesting to give some information on the prenatal screening policy in the study period in the Paris area, such as time of US and way of visualisation of the cardiac structures.”

We agree that this makes a useful addition to the paper. In the revised version, we have included a brief discussion of the prenatal screening policy for CHD in France (p. 12).

Methods:
Comment: “After exclusion 354 cases remained. What was the initial study population, how many were excluded because of associated anomalies or no informed consent? What was the total corresponding prevalence of these four CHD types?”

Response: We have now provided this information in the revised manuscript both in the text and as a detailed flow chart (p. 16).

Results:
Comment: “Please report also numbers in the tables, not just %. People will calculate back to numbers, at least I did. If numbers are less than 100, % should be reported without digits, also in the tables. Table 2 can be omitted, since the % are also reported in the text. Table 3 is confusing in its layout. The numbers refer to number of LB cases per prenatal diagnosis category, the % to the first year mortality. There were 7 LB cases after PND, of which 3 died in the first year (43%).”

Response: We have done as our reviewer has recommended. However, we prefer to keep Table 2 as part of the manuscript. We think that it provides useful information and can be an interesting result in and of itself. We defer to the editor to decide whether or not we can keep Table 2 as part of the manuscript.

Regarding reporting of percentages without digits, we can do so. However, rounding the limits of confidence intervals can become a bit problematic (lower bounds of zero) and the risk ratios will not correspond exactly to the percentages reported. We defer to our reviewer / editor whether rounding the figures further (we have used only one digit) needs to be done.

Discussion:
Comment: “Since the numbers are small, the CI intervals are wide and an decreased risk or even an increased risk of mortality in prenatally diagnosed compared to postnatally diagnosed cases can not be ruled out. For Fallot the point estimate suggests lower risk of 1st year mortality, for TGA the point estimate suggests higher risk of mortality for prenatally diagnosed cases (not close to te null as authors mentioned). Could it be that more severe cases of TGA are amenable for prenatal diagnosis, but also are at risk for infant mortality?”

Response: As above, we have acknowledged this limitation in our study (p. 10).
“Were there any other factors that may be related to mortality, such as gestational age at birth and why did the authors did not take this information into account?”
Our aim was to compare the mortality rate of newborns with one of the four CHD examined for cases diagnosed prenatally vs. those diagnosed postnatally. Our objective was not to do a “path analysis” for looking at the potential effect of prenatal diagnosis on prenatal management (including caesarean section and induction of labor), which could result in induced preterm birth or in general change the gestational age at birth for the cases diagnosed pre- vs. post-natally.
In general, as reviewer 1 has pointed out, it is possible that the potential severity of cases diagnosed prenatally (and this severity may reflect preterm births although in a previous study, we found no evidence of a higher rate of preterm birth, whether induced or spontaneous, for cases diagnosed pre- vs. post-natally (see Laas Pediatrics, 2012). In any case, the possibility of an adverse selection bias related to the severity of a given defect diagnosed pre- vs. post-natally has to be considered when one interprets the association between prenatal diagnosis and risk of mortality (Discussion, pp. 10-11).

## VERSION 2 – REVIEW

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| **REVIEWER** | Diana Wellesley<br>Wessex Clinical Genetics Service<br>Princess Anne Hospital<br>Southampton<br>SO16 5YA<br>UK |
| **REVIEW RETURNED** | 11-Sep-2017 |

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| **GENERAL COMMENTS** | Thank you for the alterations you have included. I believe all important questions have now been well addressed and I have no further recommendations. This is an interesting and useful paper. |

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| **REVIEWER** | Marian Bakker<br>University Medical Center Groningen, The Netherlands |
| **REVIEW RETURNED** | 14-Sep-2017 |

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| **GENERAL COMMENTS** | The authors have responded to the comments of the reviewers in a adequate way.<br>The paper is of high quality and interest. |