Preterm Birth and Congenital Heart Defects: A Population-based Study

**WHAT’S KNOWN ON THIS SUBJECT:** Risk of preterm birth (PTB) has been noted to be higher for newborns with congenital heart defects (CHDs). The role of associated anomalies, whether PTB is spontaneous or medically induced, or specific categories of CHDs have not been elucidated.

**WHAT THIS STUDY ADDS:** By using population-based data, we found that PTB associated with CHDs was due to spontaneous PTB. Associated anomalies accounted for a small part of this increase, and there were specific associations between categories of CHDs and PTB.

**abstract**

**BACKGROUND AND OBJECTIVES:** Preterm birth (PTB) and congenital heart defect (CHD) are 2 major causes of mortality and disability of perinatal origin. There are limited data on the relation between CHD and PTB. Our objective was to use population-based data to estimate the risk of PTB in newborns with CHD and to study specific associations between categories of CHD and PTB.

**METHODS:** We used data from a population-based cohort study of CHD (EPIdémiologique sur le devenir des enfants porteurs de CARDiopathies congénitales study), including 2189 live births with CHD (excluding isolated atrial septal defects) born between 2005 and 2008. We categorized CHD by using an anatomic and clinical classification. Data from the French National Perinatal Survey of 2003 were used to compare PTB in the EPIdémiologique sur le devenir des enfants porteurs de CARDiopathies congénitales study to that of the general population.

**RESULTS:** Of the newborns with CHD, 13.5% were preterm. The odds of PTB were twofold higher than for the general population (odds ratio 2.0, 95% confidence interval 1.6–2.5), essentially due to an increase in spontaneous PTB for newborns with CHD. The risk of PTB associated with CHD persisted after exclusion of chromosomal or other anomalies. There were significant variations in risk of PTB across the categories of CHD after adjustment for known risk factors of PTB and factors related to medical management of pregnancy and delivery.

**CONCLUSIONS:** We found a higher risk of PTB in newborns with CHD, which was essentially due to spontaneous PTB. Risk of PTB varied for categories of CHD. Our finding may be helpful for generating hypotheses about the developmental links between CHD and PTB.

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**KEY WORDS**
congenital heart defects, preterm birth, population-based study, epidemiology

**ABBREVIATIONS**
ASD—atrial septal defect  
CHD—congenital heart defect  
CI—confidence interval  
EPICARD—EPIdémiologique sur le devenir des enfants porteurs de CARDiopathies congénitales study  
IUGR—intrauterine growth restriction  
NPS—National Perinatal Survey  
OR—odds ratio  
PTB—preterm birth  
TOPFA—terminations of pregnancy for fetal anomaly  
VSD—ventricular septal defect  

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Congenital heart defects (CHDs) are the most frequent group of major congenital anomalies with a live prevalence of ∼7 per 1000 live births.¹ Despite considerable progress in their diagnosis and medical management,² CHDs remain the most important cause of infant mortality due to birth defects,³,⁴ and survivors may have short-term morbidity⁵,⁶ and adverse neurodevelopmental outcomes.⁶ An extensive literature has also documented higher risks of mortality, morbidity, and long-term adverse outcomes related to preterm birth (PTB; <37 weeks).⁷–⁹

CHD and PTB are therefore two of the leading causes of infant mortality and disability of perinatal origin.¹⁰ Although known associations exist between congenital anomalies and PTB,¹¹–¹³ few specific data exist regarding the risk of PTB for CHD. Most studies report results of hospital-based studies of the clinical management and outcomes of preterm infants with CHD.¹⁴,¹⁵ One previous population-based study reported a higher risk of PTB for newborns with CHD.¹⁰ This study did not assess the role of associated anomalies or the extent to which risk of PTB for newborns with CHD may be due to spontaneous versus medically induced PTB. Moreover, few data are available on the associations between specific categories of CHD and PTB.¹⁰

By using data from a large population-based cohort of newborns with CHD (the Etude Epidémiologique sur le devenir des enfants porteurs de Cardiopathies congénitales study; EPICARD), we estimated the risk of PTB in newborns with CHD, examined the nature of PTB (spontaneous versus medically induced PTB), and studied associations between specific categories of CHD (according to an anatomic and clinical classification¹⁶) and PTB.

**METHODS**

**Data Source**

EPICARD is a prospective cohort study of all children with 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 ≥20 weeks) diagnosed in the prenatal period or up to 1 year of age in the birth cohorts between May 1, 2005 and April 30, 2008 were eligible for inclusion. Multiple sources of data including all maternity units, pediatric cardiology and cardiac surgery centers, fetal and neonatal pathology departments, neonatal and pediatric intensive units, infant units, and outpatient clinics in greater Paris and a neighboring tertiary care center 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 ongoing and will include assessment of children’s health and neurodevelopmental outcomes until at least 7 years of age.

The total number of cases included in the EPICARD study was 2867. After excluding TOPFA (n = 466) and fetal deaths (n = 53), our initial study population comprised 2348 live births. The total number of live births in the study population base was 314,022.

Five (0.2%) cases were excluded due to missing information on gestational age (Fig 1). We also excluded isolated atrial septal defects (ASDs, n = 154) to minimize ascertainment bias. Preterm infants are more likely to undergo echocardiography resulting in diagnosis of minor ASD that may otherwise go undiagnosed. In addition, isolated minor ASD may be difficult to distinguish from patent foramen ovale. Our final study population included 2189 newborns with CHD.

Cardiac anomalies associated with a chromosomal anomaly comprised 6.1% (n = 134), and those with anomalies of other systems, including genetic syndromes, 13.9% (n = 285) of cases.

Our reference population comprised women residing in the same geographic area as that of the EPICARD population base, namely women residing in Paris and its surrounding suburbs, who were included in the French National Perinatal Survey (NPS) of 2003.⁷ The survey involved a nationally representative sample of all births in France during a 1-week period (N = 15,378), including 1821 women residing in the same geographic area as that of EPICARD. The NPS did not exclude newborns with CHD or other anomalies, which may account for ∼2% of the live births in our population.

For both the EPICARD study and the NPS, estimate of gestational age was based on medical records. By far, for most newborns in our population, this estimate is based on an early ultrasound examination.

The main outcome measure was risk of PTB. We distinguished spontaneous from medically induced PTB, by including in the latter PTB after induction of labor or cesarean delivery before labor. Risk of PTB was examined for (1) all cases, (2) all cases excluding chromosomal anomalies, and (3) cases excluding chromosomal or other anomalies.

Detailed information on diagnosis and coding of the CHD are provided elsewhere.¹⁶ To examine specific associations between categories of CHD and PTB, we used an anatomic and clinical classification of CHD, which is based on the Long List of the International
Pediatric and Congenital Cardiac Code (Table 1). This classification, the Anatomic and Clinical Classification of Congenital Heart Defects, categorizes CHD into 10 main categories and 23 subcategories by using a multidimensional approach encompassing anatomic, echocardiographic, as well as clinical and surgical management criteria. It has proved useful in a previous study aimed at assessing specific associations between a risk factor and categories of CHD.

In our analyses of the specific associations between categories of CHD and PTB, we excluded the following categories because of limited sample size: heterotaxy, including isomerism and mirror-imagery \((n = 8)\); complex anomalies of atrioventricular connections \((n = 7)\); and congenital anomalies of the coronary arteries \((n = 9)\). Hence, we compared risk of PTB for 6 categories of CHD: anomalies of the venous return \((n = 26)\), anomalies of the atrioventricular junctions and valves \((n = 109)\), functional univentricular hearts \((n = 48)\), ventricular septal defect \((VSD; n = 1396)\), anomalies of the ventricular outflow tract \((n = 47)\), and anomalies of the extrapericardial arterial trunks \((n = 124)\).

**Missing Values**

All variables had <7% missing data except for maternal occupation (19%). The probability of missing data was not statistically associated with either categories of CHD or risk of PTB.

**Statistical Analysis**

We report proportions with 95% binomial exact confidence intervals (CIs). The \(\chi^2\) or Fisher exact test were used to assess the associations between risk of PTB and maternal or fetal characteristics. To take into account the possible effect of differences in the distribution of maternal characteristics in the NPS versus our study population, we obtained standardized estimates of the proportion of PTB by using the available aggregate data on the univariable distribution of maternal age, geographic origin, maternal occupation, and parity in the NPS.

We used logistic regression to assess the association between PTB and

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**TABLE 1 Anatomic and Clinical Classification of CHD**

<table>
<thead>
<tr>
<th>CHD Categories</th>
<th>Examples</th>
<th>(n^a)</th>
<th>%</th>
<th>Prevalence(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterotaxy, including isomerism and mirror-imagery</td>
<td>Heterotaxy syndromes</td>
<td>8</td>
<td>0.3</td>
<td>0.02 (0.01–0.05)</td>
</tr>
<tr>
<td>Anomalies of the venous return</td>
<td>Anomalies of the pulmonary venous return</td>
<td>26</td>
<td>1.1</td>
<td>0.08 (0.05–0.012)</td>
</tr>
<tr>
<td>Anomalies of the atria and interatrial communications</td>
<td>Interalatrial communications ostium secundum type, patent oval foramen</td>
<td>174</td>
<td>7.4</td>
<td>0.55 (0.47–0.64)</td>
</tr>
<tr>
<td>Anomalies of the atrioventricular junctions and valves</td>
<td>Ebstein anomaly, ASD</td>
<td>109</td>
<td>4.6</td>
<td>0.35 (0.28–0.42)</td>
</tr>
<tr>
<td>Complex anomalies of atrioventricular connections</td>
<td>Congenitally corrected TGA (double discordance)</td>
<td>7</td>
<td>0.3</td>
<td>0.02 (10(^{-5})–0.04)</td>
</tr>
<tr>
<td>Functionally univentricular hearts</td>
<td>Left ventricular hypoplasia</td>
<td>48</td>
<td>2.0</td>
<td>0.15 (0.1–0.2)</td>
</tr>
<tr>
<td>VSD</td>
<td>Perimembranous VSD, muscular VSD</td>
<td>1396</td>
<td>59.4</td>
<td>4.4 (4.2–4.7)</td>
</tr>
<tr>
<td>Anomalies of the ventricular outflow tract (ventriculoarterial connections)</td>
<td>TGA, double outlet right ventricle, tetralogy of Fallot</td>
<td>447</td>
<td>19.0</td>
<td>1.4 (1.3–1.6)</td>
</tr>
<tr>
<td>Anomalies of the extrapericardial arterial trunks</td>
<td>Coarctation of the aorta</td>
<td>124</td>
<td>5.3</td>
<td>0.4 (0.3–0.5)</td>
</tr>
<tr>
<td>Congenital anomalies of the coronary arteries</td>
<td></td>
<td>9</td>
<td>0.4</td>
<td>0.03 (0.01–0.05)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2348</td>
<td>100</td>
<td>7.5 (7.2–7.8)</td>
</tr>
</tbody>
</table>

\(\chi^2\) test for homogeneity.

\(a\) Number of live births in each category in the EPICARD study.

\(b\) Live birth prevalence (per 1000 live births) in the EPICARD population, including cases of isolated ASDs.
different categories of CHD, which were included as binary predictor variables with the most frequent category (VSD) as the reference group. Potentially confounding variables taken into account included maternal age, occupation, geographic origin, parity, diabetes mellitus, vaginal bleeding, intrauterine growth restriction (IUGR; <10th percentile), and multiple births. These factors are known to be associated with risk of PTB even if their specific associations with CHD are not well documented.20

Other factors taken into account were those related to medical management of pregnancy and delivery. These included invasive prenatal testing (amniocentesis, chorionic villus sampling), prenatal diagnosis of CHD, and medical induction of labor or caesarean delivery before labor.

The Stata/SE software (version 11.0; Stata Corp, College Station, TX) was used for data analysis.

RESULTS

The live birth prevalence of CHD in our study population (n = 2189) was 7.0 per 1000 live births (95% CI 6.7–7.3). The overall proportion of PTB was 13.5%, compared with 7.2% in the general population (odds ratio (OR) 2.0, 95% CI 1.6–2.5). There were similar increases for very PTB (<32 weeks; OR 1.9, 95% CI 1.2–3.1) and moderately PTB (32–36 weeks; OR 2.0, 95% CI 1.6–2.5).

After excluding both chromosomal and other anomalies, 11.5% of newborns were PTB with an OR of 1.7 (95% CI 1.3–2.1) compared with the general population (Table 2). For newborns with major isolated CHD (≥1 CHD but no other anomalies and excluding isolated VSD), the risk of PTB was 17.5% (OR 2.7, 95% CI 2.1–3.6).

The proportion of spontaneous PTB was 9.7% (vs 3.9% in the general population, P < .001) and the proportion of medically induced PTB was 3.7% (vs 3.3% in the general population, P = .5). There was a 2.6-fold increase in the odds of spontaneous PTB for newborns with CHD compared with those in the general population (OR 2.6, 95% CI 2.0–3.5). In contrast, we found no significant increase in medically induced PTB (OR 1.1, 95% CI 0.8–1.6). The median gestational age was 35 weeks for both spontaneous and medically induced PTB (range 24–36 weeks and 27–36 weeks, respectively).

Maternal demographic and newborn characteristics of the EPICARD cohort and their association with PTB are presented in detail in Supplemental Tables 6 and 7. Mothers of newborns with CHD who were older, of African origin, unemployed, or working in administrative/public service had higher risks of PTB. Newborns of diabetic mothers or those with vaginal bleeding during pregnancy, newborns with chromosomal or other anomalies, and multiple births also had higher risks of PTB.

Specific Associations Between Categories of CHD and Risk of PTB

Risk of PTB varied significantly across the categories of CHD, ranging from 3.8% for anomalies of the venous return to 23.8% for anomalies of the atrioventricular junctions and valves (Table 4). Except for anomalies of venous return, risk of PTB was higher for all other categories of CHD when compared with VSD.

After taking into account maternal age, occupation, geographic origin, parity, diabetes, vaginal bleeding, IUGR, and multiple pregnancies, as well as factors related to medical management of pregnancy and delivery (induction of labor, caesarean delivery before onset of labor, prenatal diagnosis, invasive prenatal testing), the odds of PTB was 2.4-fold higher for anomalies of the atrioventricular junctions and valves (adjusted OR 2.4, 95% CI 1.4–4.2) and 1.6-fold higher for functionally univentricular heart (adjusted OR 1.6, 95% CI 0.7–3.9) compared with VSD (Table 5).

| TABLE 2 | Proportion of PTBs for Newborns With CHD (Excluding Isolated ASD), Compared With the General Population* |
|---------------- |--------------------------------- |---------------- |---------------- |---------------- |---------------- |---------------- |
| CHD             | n                               | Gestational Age (wk) | <32            | 32–36           | <37            | <32            | 32–36           | <37            |
|                 |                                 |                   | %              | 95% CIa          | %              | 95% CIa          | %              | 95% CIa          |
| All cases       | 2189                            |                   | 2.4            | 1.8–3.1          | 11.1           | 9.8–12.5         | <.001           | 13.5           | 12.1–15.0         | <.001           |
| Cases without chromosomal anomalies | 2055 |                   | 2.3            | 1.7–3.0          | 10.2           | 8.9–11.6         | <.001           | 12.5           | 11.4–14.0         | <.001           |
| Cases without chromosomal and/or anomalies of other systemsa | 1770 |                   | 2.1            | 1.5–2.9          | 9.4            | 8.1–10.8         | <.001           | 11.5           | 10.1–13.1         | <.001           |
| Cases without chromosomal and/or anomalies of other systems, excluding isolated VSD | 667 |                   | 3.9            | 2.6–5.6          | 13.8           | 11.1–16.5        | <.001           | 17.5           | 14.7–20.8         | <.001           |
| French NPS 2003c | 1815 |                   | 1.3            | 0.8–2.0          | 5.9            | 4.8–7.1          | 7.2            | 6.1–8.5          |

* P value for the overall χ² test comparing the distribution of gestational age (<32, 32–36, ≥37 wk) between newborns with CHD versus that of the general population (French NPS of 2003).

a P value for the χ² test comparing proportion of PTB for newborns with CHD versus that of the general population (French NPS of 2003).

b 95% binomial exact CI.

c Structural defects other than CHD.

d French NPS 2003: women residing in the same geographic area as that of the EPICARD population base (Paris and its surrounding suburbs).
TABLE 3 Proportion of Spontaneous and Medically Induced PTB (<37 wk) for Newborns With CHD

<table>
<thead>
<tr>
<th>CHD Categories</th>
<th>n</th>
<th>Spontaneous PTBs</th>
<th>Medically Induced PTBs</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>2189</td>
<td>9.7 (8.5–11.0)</td>
<td>3.7 (2.9–4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cases without chromosomal anomalies</td>
<td>2055</td>
<td>8.8 (7.6–10.1)</td>
<td>3.6 (2.8–4.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Cases without chromosomal and/or anomalies of other systemsa</td>
<td>1770</td>
<td>7.8 (6.6–9.2)</td>
<td>3.5 (2.7–4.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Cases without chromosomal and/or anomalies of other systems, excluding isolated VSD</td>
<td>867</td>
<td>12.0 (9.6–14.7)</td>
<td>5.4 (3.8–7.4)</td>
<td>.001</td>
</tr>
<tr>
<td>French NPS of 2003</td>
<td>1815</td>
<td>3.9 (3.1–4.9)</td>
<td>3.3 (2.5–4.2)</td>
<td>.001</td>
</tr>
</tbody>
</table>

a PTB after induction of labor or cesarean delivery before labor.

b 95% binomial exact CI.

c P value for the overall $\chi^2$ test comparing the proportions of spontaneous preterm, medically induced PTB and term births for newborns with CHD versus that of the general population (French NPS of 2003).

d Structural defects other than CHD.

TABLE 4 Proportion of PTB for Different Categories of CHD (Anatomic and Clinical Classification of CHD29)

<table>
<thead>
<tr>
<th>CHD Categories</th>
<th>&lt;32</th>
<th>32–36</th>
<th>&lt;37</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomalies of the venous return</td>
<td>0</td>
<td>3.8</td>
<td>3.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anomalies of the atrioventricular junctions and valves</td>
<td>4.6</td>
<td>19.2</td>
<td>23.8</td>
<td>.001</td>
</tr>
<tr>
<td>Functionally univentricular hearts</td>
<td>2.1</td>
<td>18.7</td>
<td>20.8</td>
<td>.001</td>
</tr>
<tr>
<td>VSDs</td>
<td>1.7</td>
<td>8.5</td>
<td>10.2</td>
<td>.001</td>
</tr>
<tr>
<td>Anomalies of the ventricular outflow tract</td>
<td>3.8</td>
<td>14.8</td>
<td>18.6</td>
<td>.001</td>
</tr>
<tr>
<td>Anomalies of the atrioventricular junctions and valves</td>
<td>0.8</td>
<td>18.5</td>
<td>19.3</td>
<td>.001</td>
</tr>
<tr>
<td>French NPS of 2003</td>
<td>1.3</td>
<td>5.9</td>
<td>7.2</td>
<td>.001</td>
</tr>
</tbody>
</table>

a 95% binomial exact CI.

b P value for the overall $\chi^2$ test comparing the distribution of gestational age (<32, 32–36, ≥37 wk) for categories of CHD and that of the general population (French NPS of 2003).

c P value for the overall $\chi^2$ test comparing the proportion of PTB for categories of CHD and that of the general population (French NPS of 2003).

d 97.5% 1-sided CI.

Role of Associated Anomalies

For most categories, the risk of PTB was essentially the same after exclusion of cases associated with chromosomal or other anomalies. However, for the anomalies of the atrioventricular junctions and valves, the odds of PTB decreased somewhat after exclusion of cases with associated chromosomal anomalies and for anomalies of the extrapericardial arterial trunk after exclusion of cases associated with other anomalies (detailed results available from the authors).

DISCUSSION

By using population-based data on >2000 newborns with CHD, we found a twofold increase in the overall risk of PTB in newborns with CHD compared with a reference population. This was essentially due to an increase in spontaneous PTB, and we found no evidence of an increase in medically induced PTB (induction of labor/cesarean delivery before labor). Only a small proportion (15%) of the increase in PTB was explained by associations between CHD and other anomalies. Risk of PTB was higher for certain categories of CHD, including anomalies of the ventricular outflow tract, and lower for isolated VSD and anomalies of the venous return. The higher risk of PTB for certain categories of CHD may be explained in part by their associations with other anomalies. In particular, the risk of PTB somewhat decreased for the category anomalies of the atrioventricular junctions and valves after exclusion of cases associated with chromosomal anomalies. This category includes ASDs that are known to be more frequent in newborns with Down syndrome,21 and the latter are in general at a higher risk of PTB.

To our knowledge, our study is the first to examine the nature of onset of labor for newborns with CHD and in particular the possible impact of antenatal screening on medically induced PTB. Several studies have examined the role of prenatal screening as a factor leading to induction of labor or elective cesarean delivery before term in newborns with congenital anomalies.22,23 However, in the only previous population-based study of the risk of PTB associated with CHD,10 spontaneous and medically induced PTB were not distinguished. We found...
that the higher risk of PTB in newborns with CHD was essentially due to an increase in spontaneous preterm delivery.

Our study has certain limitations. The distribution of some sociodemographic characteristics differed somewhat between our study population and that of the NPS. To take these differences into account, we standardized the proportion of PTB in our study population, by using available aggregate data on the univariable distribution of maternal age, geographic origin, maternal occupation, and parity in the NPS and found similar proportions of PTB to those reported here (detailed results available from the authors). Because this standardization was done by using the distribution of 1 variable at a time, residual confounding to differences between NPS and EPICARD in the multivariable distribution of these or other characteristics for which data were not available cannot be excluded. However, our estimate of the overall risk of PTB associated with CHD was consistent with that given by Tanner by using a different reference population.

Moreover, in our analyses of the specific associations between categories of CHD and PTB, we adjusted our estimates for sociodemographic characteristics and several other known risk factors of PTB. Nevertheless, we were not able to adjust for certain risk factors of PTB such as tobacco, alcohol consumption, and obesity, which may also be risk factors for CHD. Newborns with CHD or other congenital anomalies were not systematically excluded from the NPS. This can result in an underestimation of the true risk of PTB associated with CHD in our study because newborns with congenital anomalies tend to have a higher risk of PTB. This underestimation bias should be small or negligible, however, because newborns with congenital anomalies would comprise ~2% of the NPS.

Although our study included a large number of cases of CHD, certain categories of CHD could not be studied because of limited sample size. For certain other categories, CIs for the associations were wide, indicating the limited precision of some of our estimates.

Cases of CHD diagnosed after the first year of life may have been a source of selection bias. If there are associations between these usually minor defects and PTB, risk of PTB may be underestimated. However, given the wide availability of specialized services for pre- and postnatal diagnosis of CHD in our population, this is likely to have had a minor impact, if any, in our study. Moreover, the live birth prevalence of CHD in our study was higher than the average live birth prevalence of CHD in Europe, which suggests that diagnoses of CHD after the first year of life are unlikely to be frequent in our population.

The proportion of prenatally diagnosed cases and TOPFA tend to be higher in our population than those in other European countries. This may result in a lower proportion of PTB among newborns with CHD because our findings suggest that the more severe types of CHD, which are more likely to undergo TOPFA, tend to be at higher risk of PTB.

Our results, particularly those related to specific associations between CHD and PTB, may be helpful for generating hypotheses on the underlying mechanisms for the association between CHD and PTB. Possible mechanisms include those related to (1) existence of a common cause or risk factor, (2) clinical management of fetuses with CHD, and (3) direct or indirect effects of the CHD itself.

A genetically programmed deterioration of fetal development and the membranes may cause both CHD and PTB. Genetic disorders of the connective tissue (Marfan or Ehlers-Danlos syndrome), for example, are known for their association with CHD and may also cause PTB by a weakening, followed by preterm rupture of membranes.

A higher risk of PTB in newborns with chromosomal or other congenital anomalies has been described.
Indeed, we found that the risk of PTB for some categories of CHD was lower after excluding newborns with associated anomalies, including genetic syndromes.

There may be common environmental risk factors for both CHD and PTB. In particular, air pollution has been reported as a risk factor for CHD,\(^30\) as well as low birth weight and PTB.\(^31,32\)

Viral infection (rubella) and maternal diabetes are also known to be associated with an increase in the risk of CHD\(^33,34\) and polyhydramnios, which may result in PTB.\(^35\)

Preterm newborns are more likely to undergo echocardiography in the NICU. The associations between CHD and PTB may then be due to a diagnostic bias. We excluded isolated cases of ASD that may be particularly prone to such bias. It is worth noting, however, that, if independent of diagnostic issues, ASD is truly associated with a higher risk of PTB, we may have underestimated the risk of PTB associated with CHD by excluding the ASD.

Another explanation for the higher risk of PTB in newborns with CHD could be a higher likelihood of medically induced PTB, which has been shown to be the case for certain other congenital anomalies.\(^22,36\) However, we found no evidence of an increase for medically induced PTB for newborns with CHD.

PTB may also be a direct or indirect result of the CHD itself. Polyhydramnios, associated with fetal heart failure, may increase the risk of preterm labor\(^35\) and thus PTB. IUGR, which is known to be associated with PTB,\(^57\) is also more frequent for newborns with CHD.\(^23,38\) In our study, the proportion of PTB in newborns with IUGR was almost 20%.

We adjusted our estimates of the associations between specific categories of CHD and PTB for IUGR. However, this strategy may result in biased estimates of the association between those categories of CHD that cause both IUGR and PTB if IUGR is on the causal pathway between CHD and PTB. Nevertheless, when IUGR was excluded, the estimates of the associations between categories of CHD and PTB were essentially the same as those reported here.

The circulatory alterations associated with CHD may directly cause both IUGR and PTB. Rosenthal showed that the alteration of the fetal circulation was not compatible with optimal growth.\(^39\) Fetal growth was altered globally in cases of generalized hypoperfusion, whereas a localized low oxygen supply led to localized growth retardation. We found that the category of anomalies of the ventricular outflow tract had the highest risk of PTB. Some of the CHD in this category, particularly tetralogy of Fallot and pulmonary atresia with VSD, have been found to be associated with growth retardation,\(^40\) fetal death, and PTB.\(^10\)

In conclusion, we found a higher risk of spontaneous PTB for newborns with CHD. Risk of PTB varied significantly across categories of CHD defined based on anatomic and clinical criteria.\(^16\) Associations of CHD with chromosomal or other congenital anomalies explained only a small part of the higher risk of PTB for newborns with CHD. Our results may be helpful for generating hypotheses regarding the developmental links between PTB and CHD.

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