Incremental detection of severe congenital heart disease by fetal echocardiography following a normal second trimester ultrasound scan
Supplemental method

Primary outcome adjudication

We first identified all potential prenatal and postnatal congenital heart diseases (CHD). This first screening process was purposefully sensitive to avoid missing any cases of severe CHD (SCHD). Then, every case of CHD was independently reviewed by three investigators to identify SCHD using the algorithm detailed in Table S2. The third reviewer was an experienced pediatric cardiologist and arbitrated any disagreements. To be considered a SCHD, cases had to have diagnostic codes, clinical follow-ups and billing patterns consistent with a SCHD. For example, a baby with only one diagnostic code of tetralogy of Fallot without cardiology follow-up or cardiology imaging billing was considered a coding error and excluded. Similarly, a subject with several occurrences of a diagnostic code of a secundum atrial septal defect with, at some point, only one occurrence of a more severe CHD was also considered a coding error and excluded.

This process was done after blinding the reviewers from any prenatal data, including the need for a fetal echocardiogram (FE), its indication and its results.

Death and stillbirth certificates were first screened for all possible cardiovascular causes (Table S1) to facilitate data linkage matching. Data from these certificates was then crossmatched with administrative healthcare data, which also included the causes of death if within a hospital. The certificates were however more precise and included final autopsy results. The cause of death was then used to determine if the CHD was a contributor, as presented in Table S2.
Defining the non-inferiority margin

The non-inferiority hypothesis of an increase in sensitivity of < 5 percentage points was determined a priori. This number was based on the following elements. Firstly, while designing this study, we discussed with fetal cardiologists from Quebec and came to the consensus that an increase of only a few percentage points was deemed clinically insignificant. Secondly, we performed simulations that informed us that, according to the expected sensitivity of the 2nd-trimester ultrasound (US), the prevalence of SCHD, and the proportion of SCHD in pregnancies with risk factors, the expected gain in sensitivity would be < 5 percentage points. Thirdly, given that SCHD have a reported prevalence between 1.5 and 2.5 cases per 1,000 pregnancies, an increase of 5 percentage points would represent a small absolute number of SCHD cases. Lastly, we considered that a margin of 5 percentage point was likely to not significantly impact overall patient care because the reported variability of sensitivity by region, years of screening, operator experience and type of CHD was well above 5 percentage points.
Supplemental tables

Table S1: Initial screening list of causes of cardiovascular deaths

| ICD-10   | Description                                                                 |
|----------|-----------------------------------------------------------------------------|
| I00 – I99| Diseases of the cardiovascular system                                       |
| P29      | Cardiovascular problems occurring during the perinatal period              |
| Q20 – Q28| Congenital malformations of the circulatory system                          |
| R93.1    | Abnormal results for diagnostic imagery of the heart and coronary circulation|
| R94.3    | Abnormal results for explorations of cardiovascular function                |
| R94.38   | Abnormal results for explorations of cardiovascular function, other and non-specified |
| Y71      | Circulatory system associated with adverse incidents                       |
| Z03.5    | Under observation for suspicion of other cardiovascular problems          |
| Z13.6    | Special screening for cardiovascular problems                              |
| Z82.4    | Family history of ischemic heart diseases and other diseases of the circulatory system |

ICD10: International classification of disease 10th edition
| Primary Outcome                                           | Criteria                                                                                                                                                                                                 |
|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CHD leading to cardiovascular intervention in the first month of life | • Postnatal diagnosis of any CHD AND • At least one percutaneous or surgical intervention in the first month of life EXCLUDING • Closure of patent ductus arteriosus in preterm babies |
| CHD leading to infant mortality within the first six months of life | • Mortality in the first six months of life AND • Postnatal diagnosis of complex CHD* OR • Primary cause of death is any CHD OR • Primary cause of death is of cardiovascular nature (endocarditis, arrhythmia, etc.) with any CHD as a secondary cause of death. EXCLUDING • Premature infant with patent ductus arteriosus |
| CHD leading to termination of pregnancy, intrauterine death or stillbirth | • Prenatal diagnosis of a complex CHD* AND • No mother-child link and no indication of delivery |
| Other CHD                                                 | • Postnatal diagnosis of a complex CHD* AND • More than 5 follow-ups with a pediatric cardiologist within the first two years of life |

*Complex CHD are CHD included in the following CHD types: functionally univentricular heart, transposition of the great arteries, common arterial trunk, double outlet right ventricle, other anomalies of atroventricular or ventriculo-arterial connection, congenital aortic valve atresia, congenital pulmonary atresia, or tetralogy of Fallot. CHD: congenital heart disease.
### Table S3: Hierarchy of fetal echocardiography indications

| Hierarchy | Indication                           |
|-----------|--------------------------------------|
| 1         | Suspicion of CHD                     |
| 2         | Suboptimal cardiac image             |
| 3         | Hydrops fetalis                      |
| 4         | Extracardiac malformation            |
| 5         | Confirmed genetic anomaly            |
| 6         | Increased risk of trisomy 21         |
| 7         | Isolated single umbilical artery     |
| 8         | Hyperechogenic foci                  |
| 9         | Isolated increased nuchal translucency|
| 10        | Family history of CHD                |
| 11        | Diabetes mellitus                    |
| 12        | Maternal medication                  |
| 13        | Other                                |

CHD: congenital heart disease.