PROPOSITION DE THESE
(2 pages maximum)

SIGLE ET NOM DU LABORATOIRE : INSERM U1153
Nom de l'Équipe : Équipe d'épidémiologie Obstétricale, Périnatale et Pédiatrique (EPOpÉ)
Adresse :

Titre de la thèse : Evaluating the role of prenatal diagnosis and socioeconomic factors in the risk of infant mortality for newborns with congenital heart defects: A population-based cohort (EPICARD) study using a path analysis approach

Directeur de thèse : Babak Khoshnood
Co-tutelle :
Co-encadrant Eventuel :
Équipe :

PRESENTATION DU SUJET

Background
Congenital heart defects (CHD) are the most frequent group of major congenital anomalies, accounting for almost 1% of all births.1,2 Despite considerable progress in the medical and surgical management of CHD3-7, they remain the most important cause of infant mortality due to congenital anomalies. Moreover, survivors may have considerable short-term morbidity and long-term adverse neuro-developmental outcomes8-16. CHD represent a heterogeneous group of anomalies17-19 that may affect various aspects of the normal cardiac anatomy or function. They can be "isolated" defects (i.e., involving only one or more cardiac structures and/or the adjoining vessels (e.g., the aorta or pulmonary veins), be associated with chromosomal (e.g., Down syndrome) anomalies or those of other systems (e.g., the digestive system) or comprise one of the elements of a known syndrome (e.g., the Di George syndrome).

There is a substantial literature on various biological, clinical and epidemiological aspects of CHD. However, by far, most studies are based on data from a few specialized centres and population-based studies remain relatively rare1,3,5,20,21. The paucity of population-based data in turn limits the generalizability of available data for evaluation of the mortality, morbidity and long-term health outcomes of newborns with CHD.

Prenatal diagnosis and optimal post-natal management can result in secondary prevention of mortality and morbidity and improved long-term neuro-developmental outcomes of certain categories of CHD, notably those with transposition of great arteries3,5,9,16. However, in general, the evaluation of the impact of prenatal diagnosis on outcomes of CHD in general is empirically complicated by the fact that more severe CHD are more likely to be diagnosed prenatally. Prenatal diagnosis can also provide the opportunity for women to make an informed decision regarding their pregnancy including the option of Termination Of Pregnancy for Fetal Anomaly (TOPFA) after a prenatal diagnosis of severe, incurable CHD. TOPFA may in turn have an impact on infant mortality for newborns (live births) with CHD by reducing the number of incurable / very severe cases of CHD.

Socioeconomic differences in use of health services and health outcomes are ubiquitous and amply documented in the literature22-25. This is also true in the field of congenital anomalies where socioeconomic differences have been noted in the prevalence, prenatal diagnosis, and termination of pregnancy for fetal anomaly (TOPFA)26-30 even if much of this literature is concerned with the specific case of Down syndrome26,31-34 and very little data and none in France exist on socioeconomic differences that may exist in the prevalence, diagnosis, management or outcomes of CHD. Prenatal diagnosis and optimal post-natal management can result in secondary prevention of mortality and morbidity and improved long-term outcomes of newborns with CHD3,5,9,16. Socioeconomic disparities in prenatal diagnosis of CHD could lead to poorer outcomes of CHD for groups that may be less likely to benefit from effective access to prenatal diagnosis. In addition, prenatal diagnosis can allow the opportunity for women to make an informed decision regarding their pregnancy, including the option of Termination Of Pregnancy for Fetal Anomaly (TOPFA) after a prenatal diagnosis of severe, incurable CHD.

Objective
The aim of the present project is to evaluate the role of prenatal diagnosis and socioeconomic factors in the risk of infant mortality for newborns with CHD. We will do so based on data from a prospective, ongoing,
population-based cohort (EPICARD) study. We will explore the role and the pathways of the effects associated with socioeconomic factors and prenatal diagnosis using a path analysis (structural equations) approach by considering the possible relations between prenatal diagnosis, socioeconomic factors, other confounding and/or effect modifying factors in their associations with infant mortality. The latter is an innovative aspect of this project in that path analysis studies in our field (congenital anomalies) remain rare even if, as we intend to show as part of this project, they can make an important contribution to the field.

Outline of the chapters

1. Examine socioeconomic differences in the total and live birth prevalence of CHD and in particular severe CHD

2. Assess the relation between prenatal diagnosis and socioeconomic factors and risk of mortality for newborns with CHD, separately for each factor

3. Develop a path analysis model that examines whether the extent to which socioeconomic differences in the risk of mortality may be mediated by socioeconomic differences in prenatal diagnosis (decomposition of the total effect associated with socioeconomic factors into an indirect (that mediated by prenatal diagnosis) and a direct (other mechanisms) component.

4. Expand the path analysis model above to include another mediating variable, curative surgery that may mediate in part the relation between prenatal diagnosis and risk of mortality.

Materials and Methods

Data

This study will be based on data from a population-based, prospective ongoing cohort study: Epidemiological Study of Children with Congenital Heart Defects: A population-based study (EPICARD). The principal objectives of the study are to use population-based data from a large cohort of patients with CHD to: i) estimate the prevalence, timing of diagnosis and medical and surgical management of newborns with congenital heart defects (CHD), ii) evaluate their mortality, morbidity and neuro-developmental outcomes; and iii) identify the factors associated with their short- and long-term health outcomes, especially the impact of timing of diagnosis and the initial medical and surgical management of the infants with CHD, as well as, access to care and socioeconomic factors.

All cases (live births, Terminations of Pregnancy for Foetal Anomaly (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 ongoing and will include assessment of children’s health and neuro-developmental outcomes until at least eight years of age.

Details of coding and classification of cases for the EPICARD study are given elsewhere. Briefly, two paediatric cardiologists in the EPICARD study group attributed by consensus to each case, one, or in less than 20% of cases, two or more six-digit code(s) of the Long List of IPCCC. Cases of PDA, as well as, persistent oval foramen were excluded. Each case included in the study was then classified into one (and only one) of the ten main categories of the classification Anatomic and Clinical Classification of CHD. This classification scheme is based on a multi-dimensional approach encompassing anatomy, echocardiography, clinical and surgical management criteria. ACC-CHD includes ten main categories, ordered in accordance with the direction of blood flow, and 23 subcategories. It is designed to use the code numbers of the Long List of IPCCC but can accommodate ICD10 codes.

Statistical analysis

We will use logistic regression analysis using a counter-factual path analysis approach in order to decompose the total effects associated with socioeconomic factors into an indirect (i.e., that mediated by
prenatal diagnosis) and a direct (i.e., that possibly mediated by other factors). In addition, we will extend our path analysis approach to include more than one mediator (e.g., postnatal management, particularly surgical intervention) and add factors in the path analysis (causal diagram) that may moderate the effect of mediating variables*.

Conclusion

To our knowledge, this is the first population-based study looking at the potential mechanisms associated with the effects of socioeconomic factors on outcomes of CHD (or any other congenital anomaly). In the present doctoral project, we will expand this approach by incorporating more than one intermediate (mediator) variable and consider moderated mediation effects. This will allow us to explore possible underlying mechanisms in the pathway of socioeconomic situation. More generally, we believe that this method can also be more generally useful in looking at the outcomes of congenital anomalies and other reproductive outcomes.

PREREQUIS DEMANDE, FORMATION:

EXISTE-T-IL UN CANDIDAT POUR CETTE THESE ☑ OUI ☐ NON

NOM DU CANDIDAT : RYM EL RAIFEI
CURSUS : MASTER EN BIOLOGIE SANTE « METHODOLOGIE DES ESSAIS CLINIQUES » (MPH), Faculté de Médecine, Montpellier 1, France
DEMANDE DE CONTRAT DOCTORAL ☑ OUI ☐ NON
FINANCEMENT DU SALAIRE DU DOCTORANT PAR UNE AUTRE RESSOURCE ☐ OUI ☑ NON
SI OUI, PRECISEZ LAQUELLE :

CONTACT POUR CE SUJET : American University of Beirut Medical Center, Department of Pediatrics and Adolescent Medicine, 6th floor. P.O. BOX 11-0236 Riad El Solh 1107 2020, Beirut, Lebanon. EMAIL : RYM.ELRAFEI@GMAIL.COM
TELEPHONE : + 961 70 151140 / +961-1-350000 EXT : 5518

SPECIALITE DE LA THESE

EPIDEMIOLOGIE (AVEC EVENTUELLEMENT MENTION CLINIQUE OU SOCIALE OU GENETIQUE ☑
BIOSTATISTIQUE/BIOINFORMATIQUE ☐
INFORMATIQUE BIOMEDICALE (RECOUVRANT AUSSI L’IMAGERIE BIOMEDICALE ET LA BIOINFORMATIQUE) ☐
RECHERCHE INFIRMIERE ☐
PERFORMANCE DU SYSTEME DE SOINS ☐
AIDE A LA DECISION (DONC COUT-EFFICACITE) ☐
AUTRES (PRECISER) :

VISA DU DIRECTEUR DE L’UNITE

AVIS FAVORABLE ☑
SIGNATURE

[Signature]
Reference List


