What We Can Learn from Twins:

Congenital Heart Disease in the Danish Twin Registry

Running title: Mahle; Congenital heart disease in twins

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Our understanding of the causes of congenital heart defects has benefited tremendously from state-of-the-art genetic and epigenetic tools. The rapid progress is due in part to the development of novel, high throughput, cost effective sequencing technology – so called next generation sequencing – has made it possible to sequence the entire genome or all genes (whole exome sequencing). However, to fully understand the causes of congenital heart disease it has been important also to study population-based data that are available from large registries, which may take decades to establish. One such program has been in existence for over 60 years and has provided novel insights into the genetic and environmental mechanisms of many diseases including congenital heart defects. The Danish Twin Registry is one of the oldest twin registries in the world and it contains information about twins born in Denmark over the last more than 130 years.¹

In the current study, Christensen and colleagues analyze data from the Danish Twin study as well as the Danish National Patient Registry to examine the relationship of twin gestation on the development of congenital heart defects.² Numerous investigators have suggested that twin gestation is associated with an increased risk of birth defects, including congenital heart disease.³⁴⁵ In a large study of California birth defects surveillance program Hardin and colleagues reported that the risk of congenital heart disease was significantly increased among twins for a variety of lesions.⁶ Lesions of the outflow tract had the strongest association with twin gestation. The present study confirms this association, demonstrating rather convincingly that twin gestation carries an increased risk for most forms of congenital heart disease.

Twin studies have been particularly valuable in understanding the impact of genetic and environmental factors in the development of birth defects. When birth defects are more common among monogzygotic twins than dizygotic twins one would assume that vascular factors
including the twin-twin transfusion syndrome may contribute to congenital heart defects. Alternatively one might consider that genetic factors that contribute to the process of monozygotic twinning might also contribute to the development of congenital heart disease.

To date, there have been discrepant findings regarding the relationship of zygosity and the risk of developing congenital heart disease among twins. Most studies have suggested that birth defects are more common in monozygotic twins than dizygotic twins. Zygosity may not be easy to determine, especially in large public health datasets. Some investigators have sought to use like-sex as a proxy for zygosity. In general, like-sex twins have been reported to have higher rates of birth defects. Though such associations have varied by the type of birth defect. However, this sex-based approach has clear limitations. One of the strengths of the Danish Twin study has been the consistent use of a questionnaire to assign zygosity. When compared to cytotgenic testing this questionnaire has been shown to be highly reliable.

Unlike several other studies, the present analysis did not demonstrate a higher risk of congenital heart disease among monozygotic twins as compared to dizygotic twins. This finding has important implications for understanding the why twin gestation may be associated with birth defects including congenital heart disease. The findings of the present study would suggest that the intrauterine environment of twin gestation must somehow predispose to the development of congenital heart disease. It has been hypothesized twin gestation alters maternal nutrition to the fetus. Nutritional depletion is more common in multiple gestation. Nutrient and micronutrient intake during pregnancy has been linked to fetal congenital heart defects. This may impact not only fetal growth but potentially organogenesis as well. It is possible that such nutritional deficiency would make the fetus more susceptible to other teratogenic factors such as prenatal exposures or poor maternal health.
One controversial topic related to twin gestation relates to assisted reproductive
technology (ART). There has been increased attention focused on the possible impact of ART on
the development of birth defects. The present study did not include detailed data regarding
ART. As such, it is possible that the increased incidence of congenital heart disease among
dizygotic twins might simply reflect an increased use of ART, as ART is known to result in a
higher rate of multiple gestation births. This does not seem to be a likely explanation though for
several reasons. Firstly, the increased risk of congenital heart disease for twin gestation was
evident for several decades prior to the routine use of ART. Also recent studies have suggested
that ART does not appear to increase the risk of birth defects in twin gestation, even though it
may increase the risk in singleton gestation.

Great care has been given to the construction of the Danish Twin Registry and the Danish
National Patient Registry, nonetheless it must be recognized that the Danish National Patient
Registry identifies congenital heart lesions based on ICD codes. While the overall accuracy for
identifying congenital heart disease is high, the positive predictive value for certain lesions such
as truncus arteriosus and double outlet right ventricle in this registry is lower. The extent of
phenotyping is an important confounder in any genetic epidemiology studies and this is
particularly the case in disorders where there is substantial pleiotropy such as congenital heart
disease.

Population-based studies will continue to provide novel insights into the etiology of
congenital heart disease. Particularly valuable will be the methodologic crosslinking of such
population-based studies as Christensen and colleagues have done. One can imagine future
projects that directly link extensive registries such as the Danish Twin Study with emerging
epigenetic assays to advance our understanding of congenital heart disease and possibly to
design approaches to prevent such birth defects in the coming decades.

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**References:**


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