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—that 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 >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 past 130 years.

In the current study, Herskind et al analyze data from the Danish Twin study, and the Danish National Patient Registry, as well, to examine the relationship of twin gestation to the development of congenital heart defects. Numerous investigators have suggested that twin gestation is associated with an increased risk of birth defects, including congenital heart disease. In a large study of a 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. 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 monozygotic twins than dizygotic twins, one would assume that vascular factors including the twin-twin transfusion syndrome play a critical role in teratogenesis. Alternatively, one might consider that the 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 in dizygotic twins. Zygosity may not be easy to determine, especially in large public health data sets. 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, although 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. In comparison with cytogenetic 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 in comparison with dizygotic twins. This finding has important implications for understanding 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 that 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, because ART is known to result in a higher rate of multiple-gestation births. This does not seem to be a likely explanation, however, for several reasons. First, the increased risk of congenital heart disease for twin gestation was evident for several decades before the routine use of ART. In addition, 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 International Classification of Diseases codes. Whereas 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.\textsuperscript{13} The extent of phenotyping is an important confounder in any genetic epidemiology study, and this is particularly the case in disorders, such as congenital heart disease, where there is substantial pleiotropy.

Population-based studies will continue to provide novel insights into the etiology of congenital heart disease. Particularly valuable will be the methodologic cross-linking of such population-based studies as Herskind 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.

Disclosures

None.

References


Key words: Editorials ■ epidemiology ■ valvular heart disease, congenital
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*Circulation.* 2013;128:1173-1174; originally published online August 8, 2013;
doi: 10.1161/CIRCULATIONAHA.113.005109
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
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