Editorials

Gender differences in pediatric cardiac surgery: The surgeon's perspective

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Editorial Note: The gender initiative continues with a discussion of differences between boys and girls with congenital cardiac disease. Differences in the male/female ratio of incidence have been noted for several cardiovascular malformations. And at least one report has found that female gender per se, at a pediatric age preceding major hormonal differences, may be an independent risk factor for cardiac surgical mortality. We continue our editorial series in two months with an issue devoted to gender-related considerations in thoracic surgery.

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Women have worse outcomes after cardiac surgery.[1-5] The Society of Thoracic Surgeons National Cardiac Surgery database provides evidence that women undergoing coronary artery bypass grafting have had a significantly higher operative mortality (4.5%) compared with that of men (2.6%; $P < .0001$).[1] Multivariate analysis showed that women had higher mortality rates than equally matched men in low-risk and medium-risk groups. It was only among very high-risk patients that sex was not found to be an independent predictor of adverse outcomes. Not only is postoperative mortality higher in women, but postoperative morbidity and long-term survival are generally less favorable in women compared with men undergoing coronary bypass grafting. Women are more likely to have unfavorable preoperative profiles: they tend to be older and have diabetes, hypertension, moderate obesity, and renal disease.[2] Furthermore, women might have smaller coronary arteries and differences in coronary plaque pathophysiology and vascular endothelial function, which might affect surgical technique, midterm patency rates, and overall outcomes. Women are also known to have higher readmission rates after cardiac surgery and might have less optimal social support networks and resources during recovery periods compared with men.[3]

Does female sex-gender affect outcomes in children with heart disease? One would expect that any potential hormonal-biologic or sociocultural effects would not affect the management and outcome of infants and children with heart disease. Furthermore, numerous studies from the Congenital Heart Surgeons Society data center and large-volume pediatric cardiac units assessing the outcome after pediatric cardiac surgery do not support a gender-sex effect on outcomes.[6-19] Multi-institutional studies of the management, outcomes, and risk factors of newborns with aortic stenosis, aortic atresia, or both have shown that sex is not an independent predictor of adverse outcome.[6-8] Furthermore, sex has not been identified as a risk factor for mortality after reconstructive surgery for atrioventricular septal defects, tetralogy of Fallot, or hypoplastic left heart syndrome[9] or after the Norwood procedure for other forms of single-ventricle physiology with arch obstruction.[10] Sex has not been found to be a risk factor in neonates with pulmonary atresia–intact septum,[11] atrial isomerism–heterotaxy syndromes,[12,13] or operations for arch obstruction[14,15] or after single-ventricle palliation with modifications of the Fontan procedure.[16,17]

Despite these findings, there are some important differences between male and female patients with pediatric cardiac disease, which might in fact affect their management and surgical outcomes. Male patients have a higher incidence of hypoplastic left heart syndrome (or one of its variants) and transposition of the great

arteries, whereas in term babies patent ductus arteriosus is more common in female patients. The International Clearinghouse for Birth Defects Monitoring Systems showed that male patients had a significantly higher incidence of tetralogy of Fallot, hypoplastic left heart syndrome, and transposition of the great vessels.[20] Associated with the higher likelihood of complex congenital defects in male patients was a greater likelihood of low birth weight, prematurity, and the presence of extracardiac anomalies. Neonates with critical aortic stenosis or aortic valve atresia are 1.5 to 3 times more likely to be male. The male/female ratio of complete transposition of the great arteries is more than 2:1. Therefore one would predict that because there is a higher incidence of complex congenital anomalies and possibly associated low birth weight, prematurity, or extracardiac malformations in male patients than in female patients, the surgical outcomes should be worse for male patients.

The New England Regional Infant Cardiac Program (NERICP) published a report in 1980 that investigated the management and outcome of more than 2200 infants with heart disease between July 1968 and June 1974.[21] In the NERICP series there was a greater mortality among male infants compared with female infants. The male infants were much more likely to have D-transposition of the great arteries, hypoplastic left ventricle, heterotaxy, total anomalous pulmonary venous return, single ventricle, aortic stenosis, double-outlet right ventricle, and L-transposition of the great arteries. Female infants had a slightly higher (not significant) incidence of truncus arteriosus and atrioventricular septal defects. Although male infants overall had a higher incidence of complex cardiac lesions, female infants were more likely to have low birth weight or severe extracardiac anomalies. In this series multivariate analysis suggested that survival for female infants was poorer than would be anticipated. The report concluded that female infants with congenital heart disease were more likely to have other major noncardiac anomalies and low birth weight, consequently having a higher mortality rate than expected in the first year of life.

Since the report of the NERICP, significant improvements in prenatal diagnosis, perioperative management, surgical techniques, and postoperative cardiac care have evolved such that an increasing number of patient-specific or procedure-specific risk factors have been neutralized. As noted above, many outcomes studies have shown that no disparity in cardiovascular outcomes on the basis of sex exists in infants and children undergoing cardiac surgical palliative or reparative procedures. However, in a recent report from Chang and coworkers,[22] there is evidence to support the notion that female sex is a risk factor for in-hospital mortality among children undergoing cardiac surgery. The study reviewed discharge data from the state of California from 1995 through 1997 for children aged less than 21 years who had a cardiovascular surgical procedure (the California Office of Statewide Health Planning and Development database was used). The outcomes of more than 6500 children were evaluated to determine whether sex was an independent risk factor for pediatric cardiac surgical mortality. The overall in-hospital mortality rate was 5.2% (4.9% for male patients and 5.5% for female patients). Female patients did not appear to have higher mortality rates than male patients. Mortality was highest for neonates, followed by infants and then children aged greater than 1 year. Male patients represented a higher proportion of neonates than female patients and had more arterial switch operations, Norwood operations, aortic valve replacements, heart transplants, and aortopulmonary shunting. Female patients were more likely to have atrial septal defect closures compared with male patients. Controlling for patient-specific, procedure-specific, system, and medical variables, logistic regression analysis demonstrated that female patients had a significantly higher odds ratio for mortality than male patients (odds ratio, 1.51; $P < .01$). Thus although the crude mortality rate was slightly higher in female patients than in male patients, fewer female patients were neonates, and female patients had a larger number of low-risk procedures, such as atrial septal defect closure and a lower number of complex, high-risk procedures. After adjusting for these differences, the risk of mortality for female patients was actually 50% higher than for male patients.

The cause for a difference in outcomes for pediatric cardiac surgery on the basis of sex-gender is unclear and does not appear to be due to in-hospital use of health services and resources. The difference in outcomes might result from biologic differences, a speculation that is difficult to explain. Although a hormonal influence is unlikely, it is possible that genetic effects might result from the differences in the chromosomal complement that exists between male and female patients. A further understanding of the role of sex as a risk factor and its interaction with other variables in determining pediatric cardiac surgical outcomes remains an important area for future research.

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