Commentary: Allografts and pregnancy—Can good statistics lead to mis-conceptions about the relationship?

Jennifer S. Nelson, MD, MS

From the Division of Cardiothoracic Surgery, Department of Cardiovascular Services, Nemours Children's Hospital, Orlando, Fla.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Sept 10, 2019; revisions received Sept 10, 2019; accepted for publication Sept 11, 2019; available ahead of print Oct 18, 2019.

Address for reprints: Jennifer S. Nelson, MD, MS, Nemours Children's Hospital, 13535 Nemours Pkwy, Orlando, FL 32827 (E-mail: Jennifer.nelson@nemours.org).

J Thorac Cardiovasc Surg 2020;159:1517-8

0022-5223/\$36.00

Copyright © 2019 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.09.008>

Jennifer S. Nelson, MD, MS

Central Message

In the longitudinal evaluation of the hemodynamic effects of pregnancy, next-generation statistics need the right biomarker to deliver clinically meaningful results.

See Article page 1508.

I enjoyed reading the retrospective study by Romeo and colleagues¹ in this issue of the *Journal* in which they evaluated the effect of pregnancy on allograft conduit durability after right ventricular outflow tract reconstruction. Given that an exposure such as pregnancy is impossible to randomize and challenging to model as a temporary effect, Romeo and colleagues¹ have taken a complex study question and designed an elegant analysis. The definitions (eg, pregnancy in this study was considered delivery beyond 20 weeks gestational age) and methods were clear and thoughtful, and the study setting (The Netherlands) was conducive to excellent follow-up.

The use of mixed and joint effect models provided a robust strategy for testing the potential influence of a single pregnancy on conduit function. Specifically, Romeo and colleagues¹ measured conduit stenosis (peak gradient by standard transthoracic echocardiographic techniques) and regurgitation (significant vs nonsignificant by echocardiographic results) as conduit performance indicators over time. They then analyzed those serial measurements (from approximately 1400 echocardiograms) with a bivariate nonlinear mixed-effects model. The effect of time from the onset of pregnancy was estimated with adjusted mixed-effects submodels for both pulmonary gradient and pulmonary regurgitation. Romeo and colleagues¹ also used a Cox model to estimate the instantaneous risk of pulmonary valve replacement (PVR). They found that an increase in gradient and development of moderate or severe regurgitation increased the risk of PVR, regardless of pregnancy.

As Romeo and colleagues¹ note, the study had limited power for its primary outcome (surgical or transcatheter PVR), although the length of follow-up was good (median 15 years). In this time frame, 51 of the 165 women with allografts (31%) experienced pregnancy, and only 7 (13.7%) of those women subsequently had a PVR.

Although the authors conclude that pregnancy does not hasten conduit deterioration or PVR, the study was not designed to clarify the murky clinical connections among

pregnancy, cardiac health, and the timing of PVR. Peak conduit gradient and degree of regurgitation do not necessarily correlate with right heart function, patient symptoms, or risk of sudden death. Missing from this study of Romeo and colleagues¹ was a discussion of their institutional practice regarding indications for and timing of PVR. Congenital heart surgeons will agree that higher freedom from reintervention rates are often celebrated, but the real clinical goal for our patients after right ventricular outflow tract reconstruction is to preserve right ventricular size and function to optimize long-term outcomes. Striking the right balance is not clear-cut.

There is still lack of consensus regarding optimal timing of PVR. The past decade has seen a trend toward earlier PVR, however, and right ventricular size criteria for PVR (particularly in tetralogy of Fallot) have gained traction in many practices. We routinely follow patients after right ventricular outflow tract reconstruction with cardiac magnetic resonance imaging, and we offer PVR for patients with a right ventricular end-diastolic volume index greater than 150 mL/m².

With respect to this study, it is important to point out that Romeo and colleagues¹ do not routinely acquire cardiac magnetic resonance imaging scans of their patients and therefore do not have serial measures of right ventricular volumes. They have, however, laid the groundwork for others to take this logical next step. This study presents a nice example of underutilized statistical methods well

suited to the cardiac surgical community. Mixed and joint modeling can and should be applied with serial measurements of other biomarkers as we pursue better predictors of cardiac health.

Reference

1. Romeo JLR, Papageorgiou G, Takkenberg JJM, Roos-Hesselink JW, van Leeuwen WJ, Cornette MJM, et al. Influence of pregnancy on long-term durability of allografts in right ventricular outflow tract. *J Thorac Cardiovasc Surg*. 2020; 159:1508-16.e1.