care often requires transfer of patients between neonatal and cardiac units, further impeding comprehensive data collection.

Recent studies have explored the link between maternal disorders and CHD,[2,3] but the majority of contemporary postnatal evidence has focused on the negative associations between CHD mortality and gestational age at birth.[4-6] Despite advances in neonatal, cardiac, and cardiothoracic surgical management that continue to improve morbidity and mortality outcomes for premature infants with CHD, severe neonatal morbidities (eg, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia) still exist in this population, although true incidence of each varies between studies and by gestational age.[4-6] To fully understand the complex interplay between maternal factors, CHD, and prematurity, and to better identify specific prognostic factors for guiding therapeutic interventions and discerning outcomes, a multicenter neonatal-cardiac database that collects comprehensive prenatal, perinatal, and postnatal data throughout a hospital course is needed specifically for preterm CHD.

Paulomi M. Chaudhry, MD
Division of Neonatology
Indiana University School of Medicine
Riley Hospital for Children
Indianapolis, Indiana

Molly K. Ball, MD
Division of Neonatology
The Ohio State University Wexner Medical Center
Columbus, Ohio

Shannon E.G. Hamrick, MD
Division of Neonatology
Emory University and Children's Healthcare of Atlanta
Atlanta, Georgia

Philip T. Levy, MD
Department of Pediatrics
Harvard Medical School and Division of Newborn Medicine
Boston Children's Hospital
Boston, Massachusetts

on behalf of the Children's Hospital Neonatal Consortium Cardiac Focus Group

https://doi.org/10.1016/j.jpeds.2020.11.056

The authors declare no conflicts of interest.
Acknowledgments are available at www.jpeds.com.

References

1. Matthiesen NB, Østergaard JR, Hjortdal VE, Henriksen TB. Congenital heart defects and the risk of spontaneous preterm birth. J Pediatr 2020. http://dx.doi.org/10.1016/j.jpeds.2020.09.059.
2. Sanapo L, Donofrio MT, Ahmadzia HK, Gimovsky AC, Mohamed MA. The association of maternal hypertensive disorders with neonatal congenital heart disease: analysis of a United States cohort. J Perinatol 2020;40:1617-24.
3. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. JAMA 2015;314:1588-98.
4. Norman M, Håkansson S, Kusuda S, Vento M, Lehtonen L, Reichman B, et al. Neonatal outcomes in very preterm infants with severe congenital heart defects: an international cohort study. J Am Heart Assoc 2020;9:e015369.
5. Steurer MA, Baer RJ, Keller RL, Oltman S, Chambers CD, Norton ME, et al. gestational age and outcomes in critical congenital heart disease. Pediatrics 2017;140:e20170999.
6. Yoon YM, Bae SP, Kim Y-J, Kwak JG, Kim W-H, Song MK, et al. New modified version of the risk adjustment for congenital heart surgery category and mortality in premature infants with critical congenital heart disease. Clin Exp Pediatr 2020;63:395-401.

Reply

To the Editor:

We thank Chaudhry et al and the Children's Hospital Neonatal Consortium Cardiac Focus Group for the recognition and the interest in our recently published work. Moreover, we thank the authors for raising the important need for databases encompassing prenatal, neonatal, postnatal, and surgical data on patients with congenital heart defects. We agree that such databases are urgently needed to identify and stratify this patient population according to the risk of mortality and short-term complications such as neonatal morbidities, but also long-term complications such as neurodevelopmental disorders. Databases covering data from before to after delivery hold the potential to inform clinical practice and may ultimately provide the stepping-stones for improving outcomes.

Previous studies have indicated that prenatal factors such as fetal growth and maternal medical conditions may impact outcomes in this population.[1-3] Perinatal factors such as timing of delivery and time to neonatal surgery,[4-6] and intraoperative factors such as hematocrit have also been shown to affect outcomes.[7] However, studies have been scarce and many studies have been limited by small sample sizes, and we agree with Chaudhry et al that several gaps in the current knowledge still exist.

In Denmark, the setting of our study, several opportunities to combine individual level prenatal, perinatal, and postnatal data exist. Prenatal and perinatal data have been collected in the Danish Fetal Medicine Database (nationwide since 2011)[8] and the Danish Medical Birth Registry (nationwide since 1973).[9] Neonatal data from all Danish neonatal intensive care units are currently collected in the Danish National Quality Database for Newborns (nationwide since 2016).[10,11] Lifelong follow- up is enabled by multiple sources, including hospital diagnoses and surgical procedures stored in the Danish National Patient Registry (nationwide since 1977)[12]; prescribed medication in the Danish National Prescription Registry (nationwide since 1994)[13]; and vital status in the Civil Registration System (nationwide since 1968).[14]

We strongly encourage the formation and use of large databases of detailed prenatal and postnatal data for the benefit of patients with congenital heart defects throughout the world.

Niels B. Matthiesen, MD, PhD
Perinatal Epidemiology Research Unit
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus

Department of Pediatrics and Adolescent Medicine
Randers Regional Hospital
Randers

John R. Østergaard, MD, DMSc
Center for Rare Diseases
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus

Vibeke E. Hjortdal, MD, PhD, DMSc
Department of Cardiothoracic and Vascular Surgery
Aarhus University Hospital
Aarhus

Department of Cardiothoracic Surgery
Rigshospitalet, Copenhagen

Tine B. Henriksen, MD, PhD
Perinatal Epidemiology Research Unit
Department of Pediatrics and Adolescent Medicine
Aarhus University Hospital
Aarhus, Denmark

https://doi.org/10.1016/j.jpeds.2020.11.057

References

1. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics 2015;135:816-25.
2. Gaynor JW, Parry S, Moldenhauer JS, Simmons RA, Rychik J, Ittenbach RF, et al. The impact of the maternal-foetal environment on outcomes of surgery for congenital heart disease in neonates. Eur J Cardiothorac Surg 2018;54:348-53.
3. Hansen T, Henriksen TB, Bach CC, Matthiesen NB. Congenital heart defects and measures of prenatal brain growth: a systematic review. Pediatr Neurol 2017;72:7-18.e11.
4. Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, et al. Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy. Circulation 2009;119:709-16.
5. Lynch JM, Buckley EM, Schwab PJ, McCarthy AL, Winters ME, Busch DR, et al. Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2014;148:2181-8.
6. Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS, et al. Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Circulation 2014;129:2511-7.
7. Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, du Plessis AJ, et al. The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003;126:1765-74.
8. Ekelund CK, Kopp TI, Tabor A, Petersen OB. The Danish Fetal Medicine database. Clin Epidemiol 2016;8:479-83.
9. Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. Eur J Epidemiol 2018;33:27-36.
10. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563-91.
11. Petersen JP, Mølholm B, Cueto H, Pryds OA, Trautner S, Zachariassen G, et al. [Neonatal survival and health in Denmark]. Ugeskr Laeger 2020;182:14A.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39(7 Suppl):30-3.
13. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39(7 Suppl):38-41.
14. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541-9.

Fetal growth restriction, nutrition, and the renin-angiotensin system

To the Editor:

We read with interest the recent comprehensive review by Sehgal et al on the mechanism of fetal growth restriction (FGR)-associated hypertension, focusing on prevention and therapeutic strategies across the life course to mitigate hypertension and cardiovascular disease.[1]

Early nutrition is important. Although the prenatally activated intrarenal renin-angiotensin system (RAS) strongly contributes to FGR-associated hypertension, the review clearly showed that dealing appropriately with postnatal nutrition and nutrition in infancy can ameliorate FGR-associated hypertension. This is most important as a countermeasure for postnatal rapid weight gain (catch-up growth that occurs in small for gestational age infants because of FGR), which leads to increased insulin resistance.[2-4] Breastfeeding slows weight gain because the low protein content of breast milk (compared with infant formula) reduces circulating levels of insulin and insulin-like growth factor-I, which accelerate growth.[5] Insulin resistance also upregulates the RAS; therefore, suppressing rapid weight gain in infancy may have a favorable effect of not activating the RAS as a cause of hypertension.[6,7]

Sehgal et al also mentioned that maladaptive changes of the intrarenal RAS (increased angiotensin II and decreased angiotensin-[1-7]), independent of the systemic RAS, play an important role in the pathophysiology of FGR-induced hypertension and renal injury.[1,8]

In general, because of enhanced sodium intake systemic RAS activity is suppressed. We believe that sodium intake