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EDITORIAL COMMENT

Why Would a Cardiologist Be Interested in the Placenta?*

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I am a cardiologist, but in another life, I attended a lot of deliveries. I resuscitated neonates and taught residents to do the same. One of my quirks (I like to think of them as endearing…) was that I would insist the trainees go back after stabilizing the newborn and examine the placenta "because it was attached to the baby until a few minutes ago." Fast forward 30 years and researchers continue exploring this fascinating organ and specifically its relationship to the fetus with congenital heart disease (CHD).

In their paper in this issue of *JACC: Advances*, Desmond and Imany-Shakibai[1] report a retrospective series of placental pathology and the association of placental size with birth weight in fetuses/newborns with CHD. The placental weight to birth weight ratio (PW:BW) is inversely proportional to placental efficiency. In other words, a low PW:BW corresponds to higher placental efficiency or nutrient extraction by the fetus. PW:BW normally decreases with gestational age, and expected values for this ratio in normal pregnancies are available.[2,3] In addition to PW:BW, they also relate their findings to placental pathology-including thrombosis, infarction, chorangiosis, and hypomaturation of villi. Placental pathology is associated with hypertensive disorders of pregnancy, diabetes, and preterm birth; there is also an increase in these placental findings in CHD.[4,5] The main finding of the study is of low placental weights-unrelated to placental pathology-in pregnancies complicated by CHD but that the PW:BW ratio was disproportionately low, suggesting that fetal growth was not as compromised as one would expect based on placental size.

This is a large study, with nearly 3 times as many placental examinations as one previous paper[4] on the subject and with all placental data from a single, high-volume quaternary care center, so it is reassuring to see that findings including high percentages of pathology and low PW:BW in these pregnancies hold, including in preterm births. PW:BW ratios were less than the 3rd percentile for over half of the cohort and less than the 10th percentile for almost 80% of the cohort. The overall conclusion is that, especially when small for gestational age, CHD babies have small placentas but are well adapted to a small placenta as the PW:BW ratio is more favorable than a usual fetal growth restriction (FGR) situation.

One might expect that placental infarction, higher in CHD pregnancies, might be driving the smaller placentas. They report 20% of CHD placentas had infarcts, but this did not seem to affect their results. The issue is, however, complex—placental infarcts occur in at least 11% of otherwise normal pregnancies[6] and have been associated with maternal hypertension; in FGR pregnancies the prevalence of infarcts is even higher. And though a correlation was not observed overall in CHD, a subset of fetal CHD may indeed influence placental pathology-left side obstructive lesion placentas were more commonly affected by infarcts, a trend identified previously.[4] Importantly, in this prior work pregnancies complicated by CHD with aortic obstruction were significantly more likely to have abnormal placental pathology, and more severe brain lesions were seen when there was a placental abnormality. These data together suggest that placental pathology may have a

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compounding effect on brain injury in this high-risk population and that certain CHD lesions may be more at risk.

The authors correctly point out that there may be significant bias in the retrospective sample. Newborns were excluded if there was no placenta for examination at their institution. One quarter of the patients delivered elsewhere, very likely less complex CHD. Therefore, care must be taken in extrapolating these findings to all CHD. Furthermore, the excluded inborn cohort with no placental pathology available had more right heart defects (18% vs 9%) and fewer other anomalies (6% vs 14%) compared to included cohort. Right heart lesions have been shown to behave differently in terms of brain-sparing physiology[7,8] so this may be an issue.

Another limitation is in the grouping of CHD diagnoses. How to group CHD lesions is always a challenge. Most of the current research in fetal cardiology groups fetal structural lesions based on expected in utero changes in perfusion from the placenta to the brain and heart and whether that perfusion is antegrade or retrograde via the ductus arteriosus.[7,8] Physiologic groupings are presented by the authors, with left vs right heart obstruction and conotruncal (presumably transposition) groups showing no difference in the primary outcome. Anatomic categorization (1 vs 2 ventricles, in the authors' Supplemental material) also demonstrated no group differences. However, it is possible that grouping is obscuring a true effect, and only larger numbers of individual lesions and prospective study that includes fetal hemodynamic assessment with echocardiography and magnetic resonance imaging will be able to tease out the differences.

As a further limitation, detailed descriptive comorbidities, known to coexist in pregnancies with CHD and poor fetal growth, are presented but not included in the analysis. There were very high numbers of pregnancies affected by diabetes and hypertensive disorders-nearly 20% had gestational diabetes or hypertensive disorder of pregnancy, the latter being driven by pre-eclampsia. The cohort was also overall older than the general pregnant population. The potential for interaction of these comorbidities with the placental function and fetal growth and outcome cannot be understated.

On a related note, to what extent social determinants of health and health disparities may be influencing the results is an area not touched by this paper (they report only white vs non-white and do not include this in the analysis) but is important to consider in future studies. Adverse social conditions are associated with poor pregnancy outcomes making the influence of social determinants of health on placental health quite clear-as are associations of health disparities with outcomes in CHD.[9] However, the role of social factors in determining the health of the placenta specifically in pregnancies with CHD has not yet been thoroughly investigated.

In the end, we are left with more questions than answers: Is a dysfunctional placenta the cause of fetal CHD or an effect of abnormal placental perfusion by the fetus with an abnormal heart? Is the fetus with CHD small because it has CHD or because the placenta is small? Or are maternal, placental, and fetal vascular abnormalities intertwined at the genetic or epigenetic level? In short, is there a common origin of the maternal comorbidity, small baby and small placenta? The authors hypothesize based on the available literature and the work here is that there is likely a common developmental origin and etiology and promise further work elucidating the details.

Their findings also bring up some important practical points for consideration. Perhaps antenatal fetal surveillance and delivery planning for abnormal fetal growth with CHD should be different from antenatal management for FGR from placental insufficiency. Conversely, can we learn new ways to approach FGR by studying what in CHD pregnancies leads to a more efficient small placenta? Finally, are there interventions aimed at the maternal-placental-fetal axis that can improve longer term cardiovascular and brain health and neurodevelopmental outcomes?

I am a cardiologist and far from being a placenta expert, but maybe it's time to start going back to the delivery room to take a good long look at this amazing organ. It was after all up until moments ago a part of both the baby and the pregnant person, and is a potential window into the health of both.

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REFERENCES

1. Desmond A, Imany-Shakibai H, Wong D, et al. Prenatal congenital heart disease and placental phenotypes: preserved neonatal weight despite small placentas. *JACC: Adv*. 2023;2(4):100383.

2. Almog B, Shehata F, Aljabri S, et al. Placenta weight percentile curves for singleton and twins deliveries. *Placenta*. 2011;32(1):58–62.

3. Shehata F, Levin I, Shrim A, et al. Placenta/birthweight ratio and perinatal outcome: a retrospective cohort analysis. *BJOG*. 2011;118(6):741–747.

4. Schlatterer SD, Murnick J, Jacobs M, et al. Placental pathology and neuroimaging correlates in neonates with congenital heart disease. *Sci Rep*. 2019;9(1):4137.

5. Rychik J, Goff D, McKay E, et al. Characterization of the placenta in the newborn with congenital heart disease: distinctions based on type of cardiac malformation. *Pediatr Cardiol*. 2018;39(6):1165–1171.

6. Becroft DMO, Thompson JMD, Mitchell EA. The epidemiology of placental infarction at term. *Placenta*. 2002;23(4):343–351.

7. Hogan WJ, Moon-Grady AJ, Zhao Y, et al. Fetal cerebrovascular response to maternal hyperoxygenation in congenital heart disease: effect of cardiac physiology. *Ultrasound Obstet Gynecol*. 2021;57(5):769–775.

8. Donofrio MT, Bremer YA, Schieken RM, et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol*. 2003;24(5):436–443.

9. Peyvandi S, Baer RJ, Moon-Grady AJ, et al. Socioeconomic mediators of racial and ethnic disparities in congenital heart disease outcomes: a population-based study in California. *J Am Heart Assoc*. 2018;7(20):e010342.

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