HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2021 July 15.

Published in final edited form as:

Am J Cardiol. 2020 July 15; 127: 191–192. doi:10.1016/j.amjcard.2020.04.015.

The Case for Bringing Birthweight To Adult Cardiovascular Medicine

Bradley A. Maron, M.D.[1], **Jill L. Maron, M.D., M.P.H.**[2], **Steve H. Abman, M.D.**[3]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[2]Department of Pediatrics, Floating Hospital for Children/Tufts University School of Medicine, Boston, MA; Mother Infant Research Institute, Tufts Medical Center, Boston, MA.

[3]Department of Pediatrics, University of Colorado Anschutz School of Medicine and Children's Hospital Colorado, Aurora, CO.

Since Kannel and colleagues first reported on the association between serum cholesterol and coronary heart disease (CHD) risk in 1971,[1] identifying clinical characteristics that predict disease onset, prognosis, and treatment response has been an objective of adult cardiovascular medicine. Risk stratification tools have, in fact, revolutionized clinical practice by guiding point-of-care decision making for therapy selection and escalation in acute myocardial infarction, heart failure, pulmonary circulatory diseases, and diabetes mellitus among other treatable conditions. In the current era, risk marker discovery focuses largely on rare genetic variants and findings from biological ("-omics") platforms. Nonetheless, currently available prediction models exclude most individuals at-risk for common cardiovascular diseases.

Over the same time, gains in developmental biology have crafted a remarkable series of discoveries illustrating the importance of perinatal events in the pathogenesis of numerous adult-onset cardiac diseases. Contemporary observations show that birth weight <10% corrected for gestational age correlates strongly with adult onset cardiovascular disease, and outcomes are more severe when <5%. The major contributors to intrauterine growth restriction resulting in low birth weight include maternal preeclampsia, systemic hypertension, advanced diabetes mellitus, infection transmission, malnutrition, smoking, and alcohol or drug abuse. In industrialized nations, most infants born under these conditions survive, but at a higher risk for adult onset morbidity including cardiovascular disease, diabetes, obesity and metabolic syndrome.

This concept derived originally from data showing that high infant mortality in England and Wales in the 1920s (a period characterized by an event rate spike) correlated positively with the prevalence of coronary heart disease, but not other morbid conditions, in the same

Corresponding Author: Bradley A. Maron, M.D., 77 Ave. Louis Pasteur, NRB Rm 0630-N, Boston, MA 02067 USA, bmaron@bwh.harvard.edu.

Conflicts of Interest

Dr. Bradley Maron is a consultant for Actelion for pulmonary hypertension research. Dr. Abman is the recipient of research grants from Takeda Pharmaceuticals and United Therapeutics.

geographic region 50 years later.[2] This finding implied that environmental circumstances that increased infant mortality could adversely affect adult health among survivors. In that study, the association was particularly pronounced among younger adults, raising the specter of an unrealized association between poor standard of living in childhood and premature development of atherosclerotic disease.

Since that time, information on the perinatal-adult health continuum has matured substantially. Among adults with a CHD hospitalization or fatality in one cross-sectional study, the body-mass index (BMI) at age two was significantly lower than adults without an event.[3] Importantly, the hazard ratio associated with an increase in BMI by 1 standard deviation was 0.76 and 1.14 at ages 2 and 11, respectively, emphasizing variability in the clinical implications of body weight by lifespan stage even within the pediatric age range. Birth weight also has implications on future metabolic syndromes: in a meta-analysis involving ~152,000 individuals, the odds ratio for developing type 2 diabetes was 0.75 per kg birth weight up to ~3 kg, consistent across subpopulations in which disease onset ranged widely between 22–70 years of age.[4] However, phenotypic evidence of disease predisposition may be concealed, as body weight appears to normalize by young adulthood among most individuals with intrauterine growth restriction (due to inherited or acquired placental insufficiency disorders) or born large for gestational age (due to maternal gestational diabetes), both of which are independent predictors of future type 2 diabetes mellitus.

Maladaptive changes to the metabolic profile of vascular cells in response to low or elevated nutrient availability during development appears to underlie the pathobiological link between the extreme ends of the birth weight distribution curve and cardiovascular health. These include epigenetic and other post-transcriptional events that reprogram the injury response pattern in vascular endothelial cells, as well as dysregulate basal lipid metabolism and insulin sensitivity. For example, oxidized fatty acids and aortic atherosclerotic lesions are increased in the offspring of hypercholesterolemic animals, which may be improved by lipid-lowering therapies during pregnancy.[4] In certain instances, transgenerational epigenetic instability is traceable to specific genetic risk factors. This is the case for the enzyme methionine synthase reductase (MTTR), which regulates cellular metabolism of folate, and, therefore is important to the development of cardiovascular pathophenotypes potentially through hyperhomocysteinemia. A hypomorphic variant in *MTTR* may be transmitted across numerous generations, underscoring the perpetual ramifications of epigenetic imprinting relative to cardiovascular health.[5] More recent reports expand the range of organ systems affected by developmental biological disorders in patients to include the lung-pulmonary vascular interface. In this scenario, placental abnormalities, bronchopulmonary dysplasia, and growth restriction impair pulmonary vascular growth that can be sustained throughout childhood and lead to the early onset of pulmonary hypertension among low birthweight adults.[6]

The totality of factors that determine resilience from subacute or frank cardiovascular disease in this population is not known, although CHD associated with low birthweight does not appear contingent upon plasma cholesterol or other classical disease predictors. Further, the extent to which patients expressing an “acquired” risk factors (i.e., dyslipidemia,

systemic hypertension) due to a perinatal event is also not established. Notwithstanding these limitations, it is important to note that in 2017, ~320,000 babies were born weighing ≤2.5 kg, corresponding to ~3.2 million vulnerable individuals over a 10-year period based on birthweight alone.[7] Despite this observation, recognition of birthweight in the assessment, stratification, or management of adult patients is overlooked entirely. There are several explanations to account for this phenomenon. First and foremost, obtaining information on perinatal events has by convention been quite limited, and when available is often inaccurate. Second, knowledge of the importance of perinatal events is likely limited among internists and adult cardiologists. Third, skepticism may persist on the plausibility that childhood risk factors are pertinent to the care of adults. Fourth, a strategy to gather, interpret, and process perinatal information in clinical practice is lacking.

Importantly, these barriers are each addressable. At present, >95% of hospital systems utilize an electronic health record, suggesting that birth weight data can be made readily accessible to clinicians for virtually all patients. Operationalizing this information to raise clinician awareness is likely to require unified support among hospitals themselves, expert consensus panels, and other medical education resources. Additionally, establishing strategies that incorporate perinatal data into risk stratification tools requires retrospective and prospective clinical studies focusing on the role of therapeutic interventions toward mitigating perinatal-specific risk in cardiovascular disease. It may be the case that clinical risk related to premature atherosclerotic coronary artery disease is responsive to conventional secondary prevention medical therapy (e.g., statin treatment, others) when administered early in disease course. Alternatively, it is possible that risk modifiability in this population hinges more so on primary prevention strategies in mothers prior to birth.[8] These knowledge gaps clearly require additional, dedicated focus among investigators and clinicians alike. For these reasons, in our view it is timely to prioritize a cultural shift in medicine, defined by newfound prioritization characterizing the extent to which developmental and perinatal events may be used to optimize CHD, diabetes mellitus, and pulmonary hypertension diagnoses.

In conclusion, perinatal events may hold a key to understanding sizeable risk in adult cardiovascular disease that is unaccountable presently. Major gaps in implementing this information to the management of adult patients persists. The electronic health record provides a contemporary medium by which to begin the process of increasing awareness of this dilemma among practitioners, which must also be supported by wider efforts to define specific strategies utilizing data from the perinatal period, particularly birth weight, for optimizing timely cardiovascular disease diagnosis and, ultimately, mitigating related clinical events.

Sources of Funding

Funding to B.A.M.: 1R01HL139613-01; R21HL145420; Boston Biomedical Innovation Center, and the Cardiovascular Medical Research and Education Foundation (CMREF). Funding to SHA: NIH R01HL68702; R01HL145679; and U01HL12118.

References

1. Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. Ann Intern Med 1971;74:1–12. [PubMed: 5539274]
2. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1(8489):1077–1081. [PubMed: 2871345]
3. Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsén T, Grill V, Gudnason V, Hulman S, Hyppönen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE. Birth weight and risk of type 2 diabetes: a systematic review. JAMA 2008;300(24):2886–2897. [PubMed: 19109117]
4. Napoli C, Witztum JL, Calara F, de Nigris F, Palinski W. Maternal hypercholesterolemia enhances atherogenesis in normocholesterolemic rabbits, which is inhibited by antioxidant or lipid-lowering intervention during pregnancy: an experimental model of atherogenic mechanisms in human fetuses. Circ Res 2000;87(10):946–952. [PubMed: 11073892]
5. Padmanabhan N, Jia D, Geary-Joo C, Wu X, Ferguson-Smith AC, Fung E, Bieda MC, Snyder FF, Gravel RA, Cross JC, Watson ED. Mutation in folate metabolism causes epigenetic instability and transgenerational effects on development. Cell 2013;155(1):81–93. [PubMed: 24074862]
6. Goss K, Beshish AG, Barton GP, Haraldsdottir K, Levin TS, Tetri LH, Battiola TJ, Mulchrone AM, Pegelow DF, Palta M, Lamers LJ, Watson AM, Chesler NC, Eldridge MW. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018; 198(12):1549–1558. [PubMed: 29944842]
7. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final data for 2017. Natl Vital Stats Repor 2018;67(8):1–49.
8. van Elten TM, Karsten MDA, Geelen A, van Oers AM, van Poppel MNM, Groen H, Gemke RJBJ, Mol BW, Mutsaerts MAQ, Roseboom TJ, Hoek A; LIFEstyle study group. Effects of a preconception lifestyle intervention in obese infertile women on diet and physical activity; A secondary analysis of a randomized controlled trial. PLoS One 2018;13(11):e0206888. [PubMed: 30403756]