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Commentary on "Childhood cardiovascular health and subfertility: The Bogalusa Heart Study"

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The "common soil" hypothesis suggests that cardiovascular disease and diabetes share common genetic and environmental etiologies, and extensions of this work have since connected chronic metabolic dysregulation to wide ranging conditions from cancer to Alzheimer's disease (1). Increasing evidence also now suggests that subfertility can serve as a signal of underlying chronic disease. Might it be that infertility also falls under the influence of this "common soil"? As such, earlier detection of cardiovascular risk may serve as a prospective subfertility indicator, and pediatric screening could offer an earlier window for preventing future infertility, a condition with expensive treatment options that affects a growing proportion of men and women each year.

In this issue of *Pediatric Research*, Wang et al. explore possible links between childhood cardiovascular disease risk and subfertility in the Bogalusa Heart Study Babies sub-study (2). This study uniquely evaluated these associations to expand our understanding of the importance of cardiovascular health over the life course on subfertility in women. Overall, they found that childhood and adolescent risk factors in girls were generally not associated with indicators of self-reported fertility at about 45 years of age. Rather, pre-pregnancy systolic blood pressure was most consistently associated with multiple markers of infertility, such as indications of whether treatment was sought or whether a couple tried to conceive for over 12 months.

The results of this paper are intriguing and cause us to ask whether the "soil" sample was taken at the right time for revealing long-term infertility risk. Though lipoprotein levels, which were used to assess adolescent cardiovascular health, track reasonably well over development, levels during puberty may not be the best predictor of risk in adulthood. Longitudinal studies have shown positive predictive values of only 32.9 to 37.3% for LDL-C levels in adolescence to predict LDL-C 15–20 years later (3). This is further complicated by

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the fact that lipid levels tend to peak before puberty and decline slightly during adolescence, such that the timing of measurement may be particularly relevant. Given the controversy of pediatric lipid screening even for future risk of cardiovascular disease, the findings of this paper may suggest that early childhood and adolescence truly is not a good window for taking a “soil” sample for infertility risk. Moreover, these authors previously found more robust associations between childhood obesity (before and after age 9) and increased risk of subfertility in the same cohort (4), suggesting that lifestyle intervention to prevent continuation of pediatric obesity may potentially be more important than pharmacologic treatment for blood pressure or dyslipidemia.

It may then reasonably follow that it would be difficult to link these cardiovascular risk factors in adolescence with markers of infertility, particularly in a setting with limited markers of fertility status, and incomplete information from both partners. Importantly, the etiology of infertility is largely unknown, with about 1/3 due to male factor, 1/3 to female factor, and 1/3 to combined male/female disorders, which signals the importance of including both partners in any study assessing potentially modifiable factors and reproductive success. Preconception cardiovascular risk factors in both partners have been shown to be important for fertility, with lipid levels in men and women associated with time to pregnancy in healthy couples (5). Thus, there is a need to also understand the potential role of these pediatric cardiovascular disease risk factors in boys on male fertility and other relevant reproductive endpoints to further enable us to tease apart various etiologies of infertility and determine the best time point to intervene.

Though Wang et al. was unable to show consistent associations for pediatric risk factors, the results suggest a link between preconception blood pressure and female fertility (2). While sperm abnormalities are the leading cause of male infertility, there are several female reproductive disorders that can cause infertility including ovulation disorders (most notably polycystic ovary syndrome), endometriosis, and uterine fibroids. This makes it very difficult to identify risk factors that may influence female fertility as there are a myriad of potential pathways. And perhaps that adds to the complexity of linking cardiovascular risk factors in childhood as they likely require larger, more detailed studies to tease apart effects and pathways. Nevertheless, their results do show that an important time frame for “soil sampling” is the preconception period. Combined with the growing body of evidence for the importance of lifestyle factors during the preconception period, this finding emphasizes the need for evidence-based preconception guidance and potentially to move towards developing interventions.

While the appropriate time period for “soil sampling” remains unclear based on the currently available evidence, what is clear is that it is never too early to seek ways to improve health and well-being. The American Heart Association has appropriately emphasized the need for a life-course approach for ideal cardiovascular health and has recommended that “a premium should be placed on assisting children to maintain standards of ideal cardiovascular health early in life instead of taking a ‘wait and see’ approach by addressing or treating health and risk factors later in adulthood when they have become entrenched” (6). Life-course approaches that include both males and females are needed for understanding risk factors for

cardiovascular disease and fertility, and for helping to disentangle the complex links between lifestyle, metabolism, and fertility, and the best time to measure them.

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