Maternal Gut Virome in Pregestational Diabetes—Possible Cause of Congenital Heart Disease?

To the Editor—The role of the maternal microbiome during pregnancy on fetal and long-term health has increasingly come under scrutiny. Although a number of studies have analyzed the bacterial flora found in diabetic patients, surprisingly few have focused on the composition of the virome, whether the diversity is similar to nondiabetics, and any possible resulting interactions with health or disease.

In the paper by Kim et al [1], the authors present data on the gut virome profile of pregnant women with type 1 diabetes (T1D) versus healthy pregnant controls from the Environmental Determinants of Islet Autoimmunity (ENDIA) study. Their results are remarkable for the differential presence of viruses in the gut of the 2 study groups, particularly enteroviruses. Although women in the control group only harbored coxsackievirus (CV) A6, CVA10, and CVA14, women with T1D exclusively had CVA2, CVB4, and CVB5. Furthermore, both CVB4 and CVB5 were among the 15 most abundant viruses during pregnancy in women with T1D.

These findings are significant, because they support prior studies suggesting a potential role for viral etiologies in certain diseases. Among these, CVB infection has long been linked to T1D and myocarditis. We recently found that CVB infection during pregnancy in mice induces congenital heart disease (CHD) in the offspring, particularly when infection occurred during a critical window before fetal heart development [2]. Given that up to 50% of CHD cases have no identifiable genetic causes, the detection of previously unexplored causative mechanisms has the potential to greatly impact the detection of at-risk patients.

We have hypothesized that part of the linkage between maternal diabetes and CHD lies in increased or unique susceptibility to gut infection or colonization by certain viruses in diabetic women. Both T1D and type 2 diabetes during pregnancy are strongly associated with the development of CHD before the seventh week of gestation [3, 4]. Although the precise mechanism for this association remains unknown, most hypotheses focus on the effect of hyperglycemia on the developing heart [5]. However, results from our mouse model, as well as the observed gut virome of women with T1D in the ENDIA study, suggest that CVB infection could account for a number of the CHD observed in these pregnancies. In addition, immune compromise in T1D mothers, implied by the increased expression of picobirnaviruses, may allow pathogenic enteric viruses to proliferate with greater ease in the gastrointestinal tract and, hence, increase fetal risk [1].

These results allow us to pose the question of whether the increased risk for CHD in women with T1D is related to the altered composition of the gut virome, and particularly with the presence of CVB during pregnancy. It remains to be seen whether further studies of the maternal gut virome in different populations show similar results. Longitudinal assessment of CVB titers during pregnancy is necessary to define the natural fluctuations in viral load and detect new infections. These measurements should be carefully correlated with the development of the fetal heart and subsequently analyzed according to the observed CHD to satisfactorily test the hypothesis. In the ENDIA study, unfortunately, only a small subset of women had data from the first trimester of pregnancy, the critical window in which cardiac formation occurs and when CHD could arise. Whether the presence of the viruses later in gestation is reflective of remnants from infection earlier in pregnancy and/or whether the moms were carriers of these viruses before pregnancy would also be important questions to address.

We look forward to seeing more data from ENDIA investigators and hope to be able to collaborate with them on investigating our hypothesis. Given the high prevalence of CHD in the general (~1%) and diabetic (~5%–7%) [3, 4] population, we are certain they will have encountered a number of affected infants in their study. In addition, we would be curious as to the types of heart defects observed and association with viral titers in the stool or blood (the authors did not provide any data regarding the latter). In our mouse studies, we have found a higher proportion of heart defects with greater exposure or higher viral loads.

Again, we congratulate the ENDIA investigators for their findings and are excited about the future results. This letter bears witness as to how one area of investigation can lead to new or previously unrecognized linkages, supporting the great value of research. The possibilities for new scientific discoveries and improvements in patient care arising from such diverse investigations highlight the positive impact of our interconnected world of science.

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