Mini-commentary on "Familial aggregation of stillbirth: a pedigree analysis of a matched case control study" BJOG_22-0217

Matthew Shear[1]

[1]UCSF

August 30, 2022

JOURNAL: BJOG

DATE 08_25_2022

TITLE: Mini commentary on "Familial aggregation of stillbirth: a pedigree analysis of a matched case control study" BJOG_22-0217

Author: Matthew A. Shear, MD[a,b]

Author Affiliations:

[a] Department of Obstetrics, Gynecology, & Reproductive Sciences, University of California, San Francisco

[b] Division of Medical Genetics, Department of Pediatrics, University of California, San Francisco

Despite advances in genomics, the underlying cause of many stillbirths remains elusive. The emotional toll that a stillbirth takes on families, as well as the providers caring for them, is hard to overstate. Karyotype may identify a causative aneuploidy or large unbalanced translocation, but only in about 6% of stillbirths. Chromosomal microarray is higher yield, but still only identifies pathogenic copy number variants in about 10% of stillbirth cases (Reddy et al. N Engl J Med. 2012). The addition of exome sequencing to microarray only yielded a plausible genetic explanation in 15 out of 246 cases, or about 6% (Stanley et al. N Engl J Med. 2020). This suggested that non-mendelian mechanisms may play a significant role in stillbirth (Wojcik et al N. Engl J Med. 2020), although single gene pathogenic variants are poorly understood at the fetal level relative to the postnatal setting. The non-genetic mechanisms underlying stillbirth are also poorly understood at present, including viral infections, environmental toxins, and comorbid conditions.

Workalemahu and their colleagues present a unique analysis suggesting genomic heritability of stillbirth in some families. Using a robust matched case-control study of over 9000 stillbirths and 390 high-risk pedigrees from the Utah Population Database, they calculated the familial standardized incidence ratio and risk of stillbirth among first, second, and third-degree relatives of the pregnant individuals who had experienced stillbirth. In their adjusted model, among all relatives of an individual who experienced stillbirth, there was a relative risk of stillbirth of 1.1 (95% CI 1.00-1.22). This study adds further evidence there are heritable genetic etiologies of stillbirth not yet fully described.

Many non-genetic contributors to stillbirth risk may also cluster in families. In the present study, when adjusting for maternal race/ethnicity, socioeconomic status, and education, the elevations in stillbirth risk became attenuated, although this may be due to collinearity among variables used in the model. Health behaviors are informed through regional and family culture, leading to patterns in diet, nutrition, and exercise. These patterns contribute to modifiable health conditions known to impact stillbirth risk, including hypertension, obesity, diabetes, and smoking status. We also know the incidence of stillbirth is higher in lower income versus higher income countries, higher among individuals of lower educational attainment versus

higher education, and higher among African American and Black individuals compared to White, likely complicated by the impacts of systemic racism. This is to say nothing of the additional social determinants of health that may impact families across generations.

As Workalemahu and colleagues note, there is still much unknown about complex outcomes such as stillbirth. Their findings support that for a patient with a high-risk pedigree, genomic testing may prove informative. Future epigenetic and functional studies may help understand variants at the tissue level, and the impact of comorbidities on gene expression. Together with fetal genome sequencing, previously unexplained cases of stillbirth might be solved, improving patient counseling, and possibly changing clinical management. While genomic testing offers promise to explain a subset of stillbirths, we should not neglect the "non-mendelian" and non-genetic factors that continue to play a significant role in stillbirth risk.