Developmental milestones in early life are associated with both short- and long-term health consequences. More specifically, fetal nutrition and growth and measures of birth outcomes like weight and length at birth have been shown to have broad implications for health. Decreased gestational age at birth is associated with short-term complications, including respiratory conditions and cardiovascular complications [1, 2]. For example, early gestational age at birth of infants predicts the two largest causes of death in premature infants: underdevelopment of mature organs and bronchopulmonary dysplasia, a chronic lung disease that damages alveolar tissue. [2]. In addition, low birthweights were associated with long-term risk of developing chronic metabolic diseases like hypertension, diabetes, and other cardiovascular disease. [3-5] More generally, these findings are in line with the concept of The Developmental Origins of Health and Disease (DOHaD) [6]. Experimental work with animal models shows that restricting the nutrition, or imposing acute stress during pregnancy, replicates many of these long-term outcomes in offspring, showing that maternal physiology and metabolism during pregnancy can have lasting effects on health in the next generation. [7, 8] Gaining a better understanding of the factors that contribute to early life developmental trajectories and fetal outcomes is an important medical concern that can affect subsequent long-term health or illness.

While nutrition has received broadest attention for its role in fetal growth, there is growing evidence that the mother’s physiology and metabolism can have particularly powerful effects on fetal growth and development – stress-related maternal-placental-fetal endocrine and immune processes, in particular. Cytokines and hormones crucial in the progression of the maternal-placental-fetal interface play critical roles in key events during cellular growth, replication, and differentiation. [9] As a result, disturbances in the normal levels and amounts of exposure of these biological effectors may produce altered structure, function, and adverse outcomes. [10] Dysregulation, for example, of the hypothalamic-pituitary axis (HPA) during pregnancy is associated with increased levels of maternal, which is further associated with premature delivery and low birth weight. [11, 12] In addition, inflammatory cytokines are more likely to be released during pregnancies of mothers with hypertension as well as with chronic inflammation, also associated with suppression of growth. [13, 14] Interestingly, mothers with diabetes are actually associated with delivery of larger babies – illustrating the intricate nature of chronic maternal dysregulation and its effect on fetal outcomes. [15, 16]

One tool that holds promise to clarify the intergenerational effects of maternal physiological and metabolic state is the approach of maternal aging. Older chronological maternal age is correlated with increased rates of adverse birth outcomes, including decreased birth weight, length, head circumference, and body fat [17-21]. Pregnancy-related complications such as preeclampsia and placental disorders such as placental abruption are more likely to occur in older mothers [20, 21]. While chronological aging does provide an important measure of the aging process in mothers, age-associated deterioration and mortality risks vary between individuals of the same chronological age. For example, some individuals living in their 80’s (in terms of chronological age) may require assistance in daily activities while others with the same chronological age may continue functioning independently. This variation, also known as biological age, combines both environmental and genetic factors and may better elucidate the effect of the maternal aging process on fetal outcomes than chronological age alone [22-24]. In fact, several studies suggest that maternal biological age may impact the early developmental outcomes of offspring [25-27]. Prenatal maternal telomere length, a marker of cellular age, has been found to be associated with an increased likelihood of adverse birth outcomes [25, 27]. Nonetheless, the role of biological aging on fetal outcomes has yet to be widely explored.

Recently, epigenomic changes have emerged as accurate indicators of biological age. These measures, also known as epigenetic clocks, utilize changes in the epigenome – particularly DNA methylation (DNAm), the methylation of cytosine-phosphate-guanine (CpG) sites on DNA. These changes are more commonly known as epigenetic age and utilize epigenetic clocks that appear to serve as good proxies for biological aging across multiple physiological and functional systems. More specifically, these epigenetic clocks reflect maternal chronic stress, which provides a summary of the gestational environment of the fetus as it develops. Since these clocks can be trained on effectively any set of metabolic/physiological processes or states, they are a powerful tool to characterize these states by providing integrative, summary information on a mother’s metabolic and physiological state and measuring the “wear-and-tear” on the next generation. One small study (n = 77) among Californian women demonstrated that advanced epigenetic age is associated with early gestational age at birth and low birthweight, suggesting that epigenetic age may be predictive of adverse fetal outcomes [28]. There is, however, minimal study in a large, socioeconomically diverse population with greater rates of adverse fetal outcomes that tests the relationship between maternal epigenetic age and fetal outcomes.

The purpose of this paper is to conduct an analysis of maternal epigenetic age measured during pregnancies and birth outcomes in collaboration with the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a cohort following a large, diverse sample of women and their offspring in Cebu, Philippines for over 35 years [29]. In particular, the analysis was conducted on the pregnancies of 330 expecting female young adults and their newborn children between 2009 and 2014. To capture the maternal epigenetic age, the Hannum-EEAA, Horvath-IEAA, PhenoAge, and GrimAge clocks were utilized. For example, the acceleration of the Levine-DNAmPhenoAge clock (PhenoAge) is highly predictive of cardiovascular disease, poorer likelihood of being free of disease, and presentation of coexisting morbidities. [30] The acceleration of the Lu-DNAmGrimAge clock (GrimAge) predicts specific cardiovascular conditions, such as hypertension, Type II diabetes, and overall poorer physical functioning. [31, 32] The acceleration of both the Hannum-Extrinsic Epigenetic Age Acceleration (Hannum-EEAA) and the Horvath-Intrinsic Epigenetic Age Acceleration (Horvath-IEAA) clocks has predicted all-cause mortality. [33-35] Furthermore, accelerated placental aging measured by the Horvath-IEAA clock has also been associated with lower birthweight. [36] It was hypothesized that advanced maternal epigenetic age would be associated with adverse fetal outcomes, including decreased birthweight, length, arm circumference, head circumference, abdominal circumference, and total skin fold thickness.

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