

Should Perturbation of the Preconceptive Environment be Considered a Risk Factor for the Development of Cardiovascular Disease Later in Life?

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The concept that cardiovascular disease (CVD) has a developmental onset is not novel. This theory has been termed the *Barker Hypothesis*, *fetal programming*, *developmental programming*, *fetal origins of disease*, *thrifty phenotype*, *developmental epigenetics*, and, most recently, the *developmental origins of health and disease*. Each of these labels attempts to convey transgenerational passage of disease, through which the conceptive and gestational environment during fetal development can predispose progeny to adult disease. This approach leads to the question: Should perturbation of the preconceptive and prenatal environment be considered a risk factor for the development of CVD later in life?

Cardiovascular risk factors are traditionally divided into 2 categories: (1) *modifiable*, based on individual lifestyle choices, and (2) *nonmodifiable*, based on family history. Given Barker's work¹ and the association between maternal malnutrition and fetal origins of CVD, much of the research in the area of fetal origins of disease has been focused on maternal metabolic disparities and the development of cardiometabolic disease in adulthood. Evaluations of offspring born to women with CVD or significant cardiovascular risk have identified high incidence and susceptibility in progeny. The focus of these studies has been primarily on a direct risk factor-to-disease transmission model; for example, if the mother has a single or multiple risk factors (eg, obesity, hypertension, diabetes mellitus, hyperlipidemia, metabolic syndrome, smoker), her children are likely to develop CVD in adulthood.

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Traditional risk factors are accepted in maternal-fetal studies, whereas the physiological outcomes of unintentional maternal environmental exposures during pregnancy on fetal health are beginning to emerge.

It is well known that maternal exposure to chemical agents (eg, thalidomide) or infections (eg, Zika virus) during pregnancy can profoundly influence fetal development; therefore, it is generally accepted that perturbations of the maternal environment can affect and impair fetal health. However, the xenobiotic examples traditionally provided to make such a claim, such as those listed, are extreme and blatant. These instances provide evidence to support the concept that maternal environmental exposures and disruptions of the gestational environment can affect fetal development. Only the most severe maternal exposures may result in fetal morbidity, mortality, and teratology, whereas some subteratologic exposures may lead to more subtle fetal impairments. These impairments may predispose offspring to CVD and, in conjunction with modifiable risk factors, may culminate in reduced life span and increased progeny morbidity and mortality rates.

Although inhalation of fine and ultrafine particles has been identified as a cardiovascular risk factor,²⁻⁴ the toxicological implications of preconceptive exposures and those during pregnancy—if you'll excuse the pun—remain in their infancy. Real-world epidemiological studies and anecdotal evidence provide limited associations between air pollution and infertility⁵; however, recent studies have identified sperm DNA fragmentation and epigenetic modifications as possibly accounting for paternal transgenerational effects.^{6,7} The effect of air pollution on gamete health in the female is unclear; however, epigenetic modifications are a likely target. In rodents, preconception exposure to engineered nanomaterials (homogeneous ultrafine xenobiotic particles) increases leukocyte activity in the uterine vasculature and attenuates uterine arteriolar function at differing stages of the estrous cycle,⁸ modifying the implantation environment and culminating in delayed litter delivery.⁹

Most preconceptive studies have focused on single-sex exposures of either male or female breeding partners. In this

issue of the *Journal of the American Heart Association (JAHA)*, Wold et al focus on the fetal implications associated with preconceptive disruptions of reproductive homeostasis attributed to maternal and paternal fine particulate matter (PM_{2.5}) exposure.¹⁰ In this study, male and female mice were exposed to concentrated PM_{2.5} aerosols for 3 months before conception. Following exposures, mating, and delivery, the authors examined the ECGs, cardiomyocyte function, intracellular calcium handling, and epigenetic mediators of young male adult progeny. Although the previous studies mentioned earlier have explored developmental in utero stages, this study is the first to consider the preconceptive conditioning of both parents associated with PM_{2.5} inhalations and to identify epigenetic targets that may influence the functional cardiovascular phenotype identified in offspring.

Ambient air pollution exposure during gestation promotes fetal growth restriction,¹¹ a risk factor for the development of cardiometabolic disease based on the Barker Hypothesis. Further studies conducted during gestation report that real-world maternal exposures to air pollution and airborne particulate matter identify the development of elevated blood pressure,¹² cardiovascular malformations,¹³ and congenital heart disease¹⁴ in the children after birth. Under laboratory conditions, our group and others demonstrated genetic alterations^{15,16} along with cardiac,^{17,18} mitochondrial,¹⁷ and microvascular dysfunction¹⁹ in fetal pups after maternal particulate inhalation. These cardiovascular impairments potentiate into adulthood, leading to coronary and systemic microvascular dysfunction,²⁰ impaired bioenergetics,^{17,20} and increased susceptibility to heart failure.²¹ Cumulatively, these studies provide evidence of cardiovascular disruptions during development associated with airborne xenobiotic exposure. From these initial forays, further studies are being designed and conducted to evaluate fetal development on a continuum from preconception through adulthood to identify the critical windows of exposure.

As investigations into the developmental origins of CVD continue to be explored, we must remain conscientious regarding both traditional and novel risk factors for CVD and the importance of maternal and paternal preconceptive and prenatal health. Couples considering conception or having difficulties with fertility may want to consider environmental exposure as a component of their health concerns. Furthermore, those with extensive familial cardiovascular risk factors may want to consider limiting air pollution exposure to mitigate further cardiovascular risk to their children. Understanding the mechanisms associated with these transgenerational effects is paramount in initiating future interventional strategies, reducing fetal risk of disease, and improving health outcomes for future generations.

Disclosures

None.

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