Review

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Epigenetics: linking social and environmental exposures to preterm birth

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Preterm birth remains a leading cause of infant mortality and morbidity. Despite decades of research, marked racial and socioeconomic disparities in preterm birth persist. In the Unites States, more than 16% of African-American infants are born before 37 wk of gestation compared with less than 11% of white infants. While income and education differences predict a portion of these racial disparities, income and education are proxies of the underlying causes rather than the true cause. How these differences lead to the pathophysiology remains unknown. Beyond tobacco smoke exposure, most preterm birth investigators overlook environment exposures that often correlate with poverty. Environmental exposures to industrial contaminants track along both socioeconomic and racial/ethnic lines due to cultural variation in personal product use, diet, and residential geographical separation. Emerging evidence suggests that environmental exposure to metals and plasticizers contribute to preterm birth and epigenetic modifications. The extent to which disparities in preterm birth result from interactions between the social and physical environments that produce epigenetic modifications remains unclear. In this review, we highlight studies that report associations between environmental exposures and preterm birth as well as perinatal epigenetic sensitivity to environmental contaminants and socioeconomic stressors.

INTRODUCTION

Worldwide, 11% of infants are born preterm, defined as any birth before 37 completed weeks of gestation, leading to approximately one million deaths annually (1). Overall preterm birth rates are similar in the United States but with striking racial disparities. Over 16% of black infants are born preterm compared with less than 11% of white infants (2). Differences in socioeconomic status (3), genetics (4), and personal health behaviors (such as smoking (5) and teenage pregnancy (6)) fail to completely explain racial disparities in preterm birth. Within racial/ethnic groups, poverty is a risk factor for preterm birth (7). But income cannot "cause" prematurity and is instead a correlate of underlying causes. How poverty contributes the pathophysiology of preterm birth remains unknown. Emerging research demonstrates that preterm birth risk might be related to environmental exposures to industrial by-products such as metals and plasticizers that can leave long-lasting epigenetic marks. Epigenetic modifications in animals have been shown to persist across generations (8) and are potentially related to the phenomena of fetal programming of later life health (9). Some evidence suggests that preterm birth risk persists across generations. It is possible that epigenetic mechanisms may explain part of this observed "heritability" and could link social factors to preterm birth. However, very few studies have addressed the role of epigenetics in the pathophysiology of preterm birth. In this review, we highlight a few recent studies that support the plausibility of a role for environmental epigenetics in modifying preterm birth risk.

ENVIRONMENTAL EXPOSURES AND PRETERM BIRTH

Tobacco exposure is one of the strongest modifiable risk factors for preterm birth with smoking women having ~50% higher odds of preterm birth compared to nonsmoking women (10,11). A comprehensive Institute of Medicine report in 2006 on preterm birth summarized the evidence with respect to multiple environmental exposures. The report included analyses of air pollution, metal exposure, and other exposures and concluded that the weight of the evidence suggests that exposure to lead, sulfur dioxide from air pollution, and environmental tobacco smoke all likely contribute to preterm birth risk. The report called for further study into the environmental contributions to preterm birth. Active research has since ensued. We highlight two such intriguing studies below. The first addresses associations of exposure to toxic mixtures associated with coke production (coal manufacturing) and steel making with the risk of preterm delivery. The second investigates phthalate exposure and preterm birth.

Porter *et al.* (12) conducted a large population-based study in Alabama of over 400,000 births between 1991 and 2010. Using Alabama Department of Public Health data derived from birth certificates, the investigators geocoded infants' residential addresses and linked them to birth outcome data from the birth certificates. They identified 19 coke production and

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steel-making facilities in Alabama and obtained year-specific fugitive emissions inventories for each facility. Women living within 5 km of a plant were significantly more likely to deliver preterm (odds ratio (OR): 1.19; 95% confidence interval (CI): 1.15, 1.24) even after adjustment for race, insurance status, age, and education (OR: 1.05; 95% CI: 1.01, 1.09). The investigators then stratified by high vs. low (above or below the median) emissions of several substances from these plants. Women living within 5 km of plants with high emissions of a mixture of volatile organic compounds (benzene, toluene, ethylbenzene, and xylene) (OR: 1.09; 95% CI: 0.99, 1.20), or a mixture of metals including arsenic, cadmium, lead, manganese, and mercury (OR: 1.07; 95% CI: 1.01,1.14), had higher odds of preterm birth compared to women living further away. However, for women living within 5 km of lower emitting plants, there was no increased risk of preterm birth (ORs ranged from 0.84 to 1.04). While this study was limited by lack of data on smoking or personal exposure measurements, its results are striking. Given that minority and poor women are more likely to reside close to industrial sites, environmental exposures may partially explain why black and poor women have a higher risk of preterm birth. Furthermore, the socioeconomic status of neighborhoods in close proximity to high vs. low emitting plants would not be expected to differ greatly, suggesting that the contaminants themselves (not other factors associated with poverty) might be causally linked to preterm birth.

Another set of chemicals gaining attention as reproductive toxicants are phthalates. Phthalates are plasticizers and solvents commonly found in foods (13) and personal care products (14). Dietary exposure to phthalates comes primarily from the food packaging and includes both high-molecular-weight phthalates (bis(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate, and butyl benzyl phthalate) and low-molecular-weight phthalates (dimethyl phthalate and diethyl phthalate) (15). Personal care products that contain phthalates include lotions, perfumes, and cosmetics which contain diethyl phthalate and dibutyl phthalate (16). Additionally, vinyl flooring contains DEHP and butyl benzyl phthalate and can cause household or workplace exposure (16). Thus, phthalate exposure is ubiquitous, and phthalate levels have been detected in most pregnant women in the United States (17,18) and abroad (19,20). Ferguson *et al.* performed a prospective, nested case–control study of 130 preterm and 352 term births at a Massachusetts birth hospital. Pregnant women provided three urine samples during pregnancy, and nine phthalate metabolites were measured. The geometric mean of the three samples was used to determine a woman's phthalate exposure. Women with higher levels of several metabolites had higher odds of preterm birth even after adjustment for maternal age, race/ethnicity, education, and specific gravity of the urine at the time of collection. Per natural log increase, women had higher odds of preterm birth associated with mono-(2-ethyl)-hexyl phthalate (OR: 1.32(1.07–1.68)), mono-(2-ethyl-5-carboxypentyl) phthalate (OR: 1.40 (1.13–1.74)), and the molar sums of DEHP metabolites (∑ DEHP; OR: 1.33 (1.04–1.70)). A subgroup analysis of preterm births that were spontaneous (due to preterm premature rupture of membranes or preterm labor) revealed potentially stronger associations. For example, per natural log increase of ∑ DEHP, the OR for spontaneous preterm birth was 1.63 (1.15–2.31). Similar to exposure to industrial sites, exposure to phthalates is not equally distributed through the population. The environment, dietary practices, and cultural practices may put poor and minority women at higher risk of exposure to certain phthalates (21). Whether differential phthalate exposure is causally related to preterm birth disparities is unknown but worthy of study, especially given biologic evidence that such exposures might alter epigenetic marks (22,23).

ENVIRONMENTAL EPIGENTICS

Epigenetics refers to alterations in chromatin structure that can affect gene expression independent of DNA sequence variation (24). Several studies have linked dietary and environmental exposures to epigenetic alterations in humans. While there are numerous epigenetic mechanisms, in this review, we highlighted two landmark studies suggesting that one particular mechanism, DNA methylation, is modifiable in humans *in utero*.

Heijmans *et al.* (25) were among the first to provide epidemiologic evidence that changes in epigenetic marks in humans might arise from fetal exposures and persist a lifetime. They studied 112 individuals exposed as fetuses to the Dutch Hunger Winter in 1945–1946, and 122 same-sex siblings who were not exposed to the famine as fetuses. They obtained blood from these participants 60 y later and analyzed DNA methylation of the insulin-like growth factor II gene (*IGF2*), an imprinted gene with a well-defined differentially methylated region that helps regulates expression. The individuals in the study who were exposed to famine during the periconceptional period ($n = 60$) had significantly lower methylation of the *IGF2* differentially methylated region compared to their siblings (48.8 vs. 51.5%; $P = 1.5 \times 10^{-5}$). Exposure later in gestation was not associated with differential DNA methylation. These findings were notable because of rapid DNA demethylation and remethylation that occurs at the time of conception (26). The periconceptual environment may represent a window of vulnerability during which differential methylation could occur in response to a severe environmental stimulus.

Tobacco use during pregnancy represents one of the most-studied and well-established toxic risk factors for several birth outcomes including preterm birth and intrauterine growth restriction (10). How smoking leads to biologic alterations in the fetus remains unclear. Joubert *et al.* conducted an epigenome-wide association study or "EWAS" discovery analysis in 1,062 participants of the Norwegian Mother and Child Cohort Study (MoBa) to identify candidate methylation loci associated with maternal smoking in pregnancy. The top hits underwent a replication analysis in the Newborn Epigenetics Study in North Carolina (27). The investigators used the Illumina Infinium HumanMethylation450 BeadChip array that analyzes DNA methylation of more than ~450,000 sites. After multiple comparison adjustment, they found 26 CpG sites in cord blood that were significantly associated with maternal cotinine concentrations and maternal self-report of smoking in Norwegian

Mother and Child Cohort Study (MoBa). Top sites from three of the genes (*AHRR*, *CYP1A1*, and *GFI1*) were then tested and replicated in a smaller subset of Newborn Epigenetics Study participants. The Joubert study marked the beginning of other large-scale perinatal epigenomic studies that have thus far focused on smoking (28) and birth weight (29) but hold the promise of expanding to other exposures and outcomes.

Animal models suggest that other toxins (in addition to tobacco) likely induce epigenetic modifications. Li *et al.* studied the impact of the phthalate metabolite DEHP during pregnancy on DNA methylation of imprinted mouse genes in the offspring and in the subsequent generation. They found significantly lower DNA methylation that persisted for two generations in both *Igf2r* and *Peg3* (30). The agouti mouse model has led to insights regarding environmental effects on DNA methylation and phenotype. The agouti mouse has a well-characterized metastable epigenetic allele in the agouti gene. Methylation *in utero* can be modified by diet, and investigators can produce markedly different phenotypes (including yellow vs. brown coat color, obese vs. lean body habitus, and tumor-prone vs. cancer free) by altering methyl donor concentrations in pregnant dams even when postlactation diets are identical (31–33). Dolinoy *et al.* (32) exposed pregnant and lactating agouti mice to bisphenol A and observed lower DNA methylation of the same metastable epiallele A^{vy} locus in the promoter region of the agouti gene as found in studies of methyl donor and obesity phenotypes. This finding suggests that chemicals may impact allele-specific methylation. Of particular interest, the effect of bisphenol A on the mouse phenotype and DNA hypomethylation was reversed with dietary intervention with methyl donors or the phytoestrogen genistein. Taken together, these animal studies suggest that toxins affect epigenetic modifications and that these marks may persist for generations but could be reversible.

TRANSGENERATIONAL TRANSMISSION OF PRETERM BIRTH RISK

Whether epigenetics marks in humans are inherited transgenerationally is an area of active research (34). This naturally begs the question of whether preterm birth risk might be inherited transgenerationally and whether epigenetic mechanisms mediate this risk transmission. If so, preterm birth risk, if uninterrupted, could lead to a cycle of worsening health risks with subsequent generations. Disentangling potential epigenetic heritability effects from genetic heritability will be difficult, but given that epigenetic marks are potentially modifiable, the potential benefits necessitate this line of research.

Several large population-based studies have demonstrated modestly elevated risk of delivering preterm if a mother herself had been preterm (**Table 1**) (35–37). Women born preterm might have a higher risk of preterm birth due to shared biologic/genetic characteristics of their mothers or similar social/environmental exposures that their mothers also experienced when they were pregnant a generation prior. Or perhaps, fetal exposure to an inflamed intrauterine environment or physiologic stressors in early infancy leads to a phenotype that persists throughout childhood and adolescence and results in a higher risk of preterm birth. Whether unique transferable epigenetic marks are set in germ cells after prematurity is only beginning to be studied. Cross-sectional studies of cord blood of preterm neonates reveal distinct DNA methylation profiles from term infants (38,39). Whether these differences would also be present if the fetuses of the same gestational age were compared to the preterm infants has not been studied. Additionally, whether differences in methylation among preterm vs. term infants persist into childhood and beyond remains unknown.

Table 1. Studies of transgenerational preterm birth risk among former preterm vs. term mothers

Studies	*n*	OR	95% CI
Selling *et al.* (31) (Sweden)	38,720	1.24	0.95–1.62
Klebanoff *et al.* (30) (Denmark)	1,298	1.5	0.9–2.5
Castrillo *et al.* (32) (Illinois)			
White	110,338	1.3[a]	1.1–1.4
Black	32,986	1.1[a]	1.1–1.2

CI, confidence interval; OR, odds ratio.
[a]Risk ratio (instead of odds ratio).

Transgenerational inheritance of preterm birth risk may represent a legacy of social and environmental exposure. Collins *et al.* (40) studied over 40,000 African-American infants' birth records in Illinois and linked them to births of their mothers in Chicago. Independent of their mothers' residential environments, maternal grandmothers' exposure to neighborhood poverty independently predicted infant low birth weight (<2,500 g; OR: 1.3; 95% CI: 1.1, 1.4). While low birth weight is a composite outcome of both preterm and small term infants, it is often used due to the reliability of birth weight from vital records when compared to gestational age assessments. This study hints at the concept of fetal programming of later health and disease. While the developmental origins of health and disease hypothesis has been well established for cardiovascular and metabolic health (41), this study supports continued investigation into fetal origins of pregnancy outcomes in subsequent generations.

One troubling aspect of preterm birth risk is the erosion of immigrant health status over generations in the United States. This finding is more consistent with epigenetic inheritance than genetic inheritance of prematurity. A landmark paper by David and Collins in 1997 demonstrated that African-born black women had similar risk of delivering low-birth-weight infants compared with white Americans and that these rates were substantially lower than that for US-born black women (4). This study highlighted several important tenants of perinatal disparities. First, genetics is unlikely to be responsible for worse birth outcomes among African Americans compared with white Americans given that US-born black women are likely to be more genetically similar to white Americans (due to generations of racial mixing) than African-born black women would be to white Americans (42). Second, the risk of preterm birth is modifiable. Part of this modifiability likely resides at the intersection of culture and individual choice (smoking, diet, exercise, and sexual health). However, societal changes

are also needed not only to tackle issues of poverty and the increased psychosocial stress that typically accompanies it but also to mitigate the environmental exposures from pollutants such as metals and potentially phthalates, some of which might track with socioeconomic status (21). Improving the perinatal environment may prove to be critical in the long term, given that reductions in toxic exposures may affect more than just the individual fetus exposed but also generations to come.

CONCLUSIONS AND FUTURE DIRECTIONS

Preterm birth risk tracks with social disadvantage, but how black race or poverty leads to preterm birth remains a research need. Recent evidence that environmental exposures affect preterm birth risk and lead to epigenetic modifications suggests that epigenetics may play a role in connecting the social and toxic environments to preterm birth. Furthermore, differential risks for preterm birth among recent African immigrants compared to black Americans suggests that an individual's inherited biology (beyond genetic code) may be due to acquired heritability rather than genetic heritability. Our risk for prematurity may reach back to epigenetic marks modified during the conception of our mothers or even earlier. Exploration into perinatal exposures that affect fetal epigenetics is just the first step of a field of research that ultimately needs to discover which epigenetic modifications remain throughout the lifetime thereby affecting reproductive health. Investigating the epigenetic contributions to preterm birth will require careful studies of preterm birth subtypes (spontaneous vs. medically indicated) and then further delineation into underlying causes of these subtypes (preterm labor, preterm premature rupture of membranes, cervical incompetence, preeclampsia, and poor fetal growth). To understand the molecular events leading to preterm birth subtypes, relevant target tissues should be queried and include placenta, cervix, and uterus (when available). Additionally, studies of preterm offspring tissues beyond umbilical cord blood, including urine, sperm (in adulthood), sputum, nasal cells, are required to determine the impact of epigenetic marks on long-term health. Finally, epigenetic epidemiology is starting to move beyond investigations of just DNA methylation alone. Recent studies of microRNAs (43,44) are emerging in the perinatal literature and should continue, as should the study of other noncoding RNAs and histone modifications. Studying more than one mechanism simultaneously will lead not only to better understanding of mechanisms but also holds the promise of leading to targeted interventions to interrupt the cascades that lead to preterm birth and its sequelae.

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