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# Environmental Factors Involved in Maternal Morbidity and Mortality

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## Abstract

Nongenetic, environmental factors contribute to maternal morbidity and mortality through chemical exposures via air, water, soil, food, and consumer products. Pregnancy represents a particularly sensitive window of susceptibility during which physiological changes to every major organ system increase sensitivity to chemicals that can impact a woman's long-term health. Nonchemical stressors, such as low socioeconomic status, may exacerbate the effects of chemical exposures on maternal health. Racial/ethnic minorities are exposed disproportionately to both chemicals and nonchemical stressors, which likely contribute to the observed health disparities for maternal morbidities and mortality. Epidemiological studies linking exposures to adverse maternal health outcomes underscore the importance of environmental health impacts, and mechanistic studies in model systems reveal how chemicals perturb biological pathways and processes. Environmental stressors are associated with a variety of immediate maternal health impacts, including hypertensive disorders of pregnancy, fibroids, and infertility, as well as long-term maternal health impacts, such as higher risk of breast cancer and metabolic disorders. Identifying and reducing a pregnant woman's environmental exposures is not only beneficial to her offspring but also important to preserve her short- and long-term health.

**Keywords:** environmental exposures, maternal health, window of susceptibility, air pollution, endocrine-disrupting chemical

## Introduction

Research on environmental exposures of pregnant women has focused on adverse health effects in their offspring, but relatively few studies have focused on the short- and long-term health of the mother. Preexisting conditions with links to environmental exposures and maternal gestational exposures pose risks to women's health both during pregnancy and after parturition. Environmental toxicants that play a role in maternal health are ubiquitous, with well over 70% of reproductive-age women and pregnant women having detectable levels of phenols, such as bisphenol A,

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Table 1. Examples of Environmental Stressors Linked to Maternal Health Outcomes and Potential Moderating Factors[a]

| *Environmental stressors* | *Maternal outcomes* |
|---|---|
| Air pollution | Hypertensive disorders of pregnancy[3,4] |
| | Polycystic ovarian syndrome[5] |
| | Subfertility[6–9] |
| | Miscarriage[10,11] |
| | ART failure[12–17] |
| Metals | Hypertensive disorders of pregnancy[18,19] |
| | Uterine fibroids[20–23] |
| | Subfertility[24–26] |
| | Miscarriage[27,28] |
| | Cardiometabolic health[29] |
| PFAS[a] | Breast development and lactation[30–32] |
| | Breast cancer[33,34] |
| | Cardiometabolic health[35] |
| Persistent pesticides (DDT and DDE) | Lactation impairment[36] |
| | Breast cancer risk in mother and female offspring[37] |
| Persistent pollutants (dioxin/PCBs) | Breast cancer risk in mother by 50 years of age[38] |
| | Mammary development and lactation[39] |
| EDCs (*e.g.*, phthalates, phenols) | Uterine fibroids[40–42] |
| | Thyroid function, glucose metabolism and obesity, fertility, and carcinogenesis[43] |
| Potential moderators | |
| Race/ethnicity | Cardiometabolic health[44] |
| | Uterine fibroids[45] |

[a]Most exposures were associated with more adverse outcomes, but the strength and direction of effect varies. See cited references for details.

ART, assisted reproductive technology; DDE, dichlorodiphenyl dichloroethene; DDT, dichlorodiphenyltrichloroethane; EDC, endocrine-disrupting chemical; PCB, polychlorinated biphenyl; PFAS, perfluoroalkyl substance.

persistent organic pollutants (POPs), and polycyclic aromatic hydrocarbons.[1] Levels of these toxicants are often higher in nonwhite women[2]; and these chemical stressors, in combination with nonchemical stressors, such as neighborhood conditions, contribute to health disparities in maternal morbidity and mortality, as well as to long-term postpregnancy health. In this review, we consider the role of environmental exposures on fertility, pregnancy, maternal morbidities, and women's health beyond the postpartum period. Examples from both environmental epidemiology and fundamental mechanistic research demonstrate a direct role of the environment during this window of susceptibility, as well as indirect impacts on comorbidities or health effects later in life (summarized in Table 1).

## Maternal Environmental Health Disparities

A health disparity refers to differences in the prevalence of health conditions that adversely affect disadvantaged populations.[46] In the United States, racial/ethnic minorities, socioeconomically disadvantaged populations, underserved rural populations, and sexual and gender minorities are included in this definition. Often these populations experience higher disease incidence or prevalence, earlier onset, more aggressive progression, and premature or higher mortality.[46]

Chemical and nonchemical exposures that adversely affect maternal health are not randomly distributed across the population; their distribution contributes to the widespread disparities observed across the health conditions described in this review. For example, racial/ethnic minorities live in largely different physical and social environments compared with the majority white population,[47] and racial differences in exposure to stressors emanating from institutional, personally mediated, and internalized discriminatory policies and practices lead to differential risk across the life span, including during the reproductive period.[48] Such conditions may subsequently contribute to the disproportionately increased risk of adverse maternal health behaviors (*e.g.*, disrupted sleep) and outcomes (*e.g.*, preeclampsia), along with a cascade of suboptimal health consequences (*e.g.*, cardiovascular disease).[2,49–51] Chemical exposures are higher, or their reported associations tend to be stronger, among racial/ethnic minorities compared to white populations for cardiometabolic health outcomes, such as obesity, hypertension, type 2 diabetes mellitus, chronic kidney disease, and cardiovascular disease.[2,20,52–58] For example, a recent review of the effects of synthetic chemicals on cardiometabolic health among vulnerable populations (defined broadly as pregnant women and children, the economically disadvantaged, and racial/ethnic minorities) found associations of some POPs (*e.g.*, perfluoroalkyl/polyfluoroalkyl substances) and non-POPs (*i.e.*, phenols, phthalates, and parabens) with gestational diabetes and dysregulated glucose metabolism.[44]

Racial/ethnic minority women generally have a higher body burden of exposures from consumer products, occupations, and residential characteristics.[50,51] Exposure to potentially dangerous beauty product-related chemicals during reproductive ages can result from discriminatory practices and policies related to the marketing of chemical products to racial/ethnic minorities (*e.g.*, hair relaxers with lye) and product preferences to achieve a culturally desirable Eurocentric beauty standard will influence product uptake/usage of hair relaxers and skin lighteners.[57] Disparate exposure to endocrine-disrupting chemicals (EDCs) can occur through discriminatory racial residential and labor market segregation policies and practices. Such practices place racial/ethnic minorities in closer proximity to sources of water and air pollution, and these minorities are less likely to benefit from remediation efforts after contamination is identified in a community.[59] Higher consumption of EDC-containing processed foods is due to ''food deserts'' or ''food swamps,'' with fewer healthy options available in low-income neighborhoods. Limited resources also drive the purchasing of cheaper, more chemically laden consumer products.[56] An important pursuit of minority health research is to identify health burdens of racial/ethnic minority groups that stem from environmental exposures and social disadvantages arising from discriminatory policies and practices that contribute to maternal health disparities.[46]

## Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy (HDP) comprise a spectrum of pregnancy complications that include gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with/without superimposed preeclampsia and are leading causes of maternal morbidity and mortality.[60] In addition to

pregnancy and postpartum complications, women who experience HDP are at significantly higher risk for diseases later in life.[61,62] Risk factors for HDP include comorbidities (*e.g.*, diabetes) and maternal age >40 years; however, most cases of preeclampsia (the most common type of HDP) occur among first-time pregnancies with no other known risk factors,[63] suggesting a potential role of environmental exposures.

Air pollution has been the primary focus of many studies of HDP. Traffic emissions (*e.g.*, particulate matter, nitrogen oxides) have been classified by the National Toxicology Program as a presumed hazard for HDP.[3] Fewer studies have evaluated other environmental contaminants, limiting the ability to draw definitive conclusions. Evidence of an association with preeclampsia exists for cadmium and other heavy metals, POPs such as perfluoroalkyl substances (PFAS), and plasticizers (*e.g.*, phthalates).[18,64] Despite the disproportionate burden of chemical exposures, few studies of HDP or other cardiometabolic health outcomes have focused on racial/ethnic minority populations.[44]

The clinical manifestations of preeclampsia are largely attributed to (i) placental dysfunction due to incomplete remodeling of the uterine spiral arteries early in pregnancy and subsequent reduction of blood supply and nutrients to the fetoplacental unit; and (ii) dysregulated maternal hemodynamics. Numerous environmental factors plausibly could contribute to the onset and/or progression of either of these processes.

Remodeling of the spiral arteries is critical to the proper exchange of oxygen and nutrients to the fetus and removal of waste from the fetus during pregnancy. Improper remodeling leads to hypoxia of the placenta and the subsequent release of factors that activate oxidative stress and inflammation pathways. Many environmental contaminants cross the placenta and can disrupt the proper trophoblast migration and invasion necessary for spiral artery remodeling and, thus, normal placentation.[65,66] Epidemiologic studies demonstrate associations between contaminant exposures and angiogenic factors that are strong biomarkers of implantation and placental development[67,68] and epigenetic changes that may reflect perturbations in normal processes.[69]

Many environmental contaminants, particularly air pollutants and heavy metals, have been linked to elevated blood pressure in both pregnant and nonpregnant populations.[3,70] In response to the growing demands of the fetus, maternal hormones mediate hemodynamic changes to increase blood volume and cardiac output while decreasing vascular resistance. Furthermore, endothelial cells play a critical role in these processes by sensing blood composition and by providing a physical barrier to the improper movement of water, ions, proteins, and cells from the blood into the vessel walls. Oxidative stress and inflammation play a causal role in endothelial cell dysfunction,[71] and these pathways may be highly sensitive to environmental exposures. Epidemiologic evidence linking environmental exposures to HDP and the biological plausibility based on mechanistic studies support an important role for the environment in the etiology of HDP.

### Breast Development and Health

The breast has the longest developmental window of any organ in women; beginning in the early prenatal period, continuing throughout puberty, with completion during the first full-term pregnancy.[72] During pregnancy, the breast is particularly vulnerable to toxicant exposure as the body is undergoing complex changes in nutrient and toxicant metabolism and hormonal shifts.[73–75] Pregnancy as a window of susceptibility for toxicant exposure adversely altering the human breast is understudied.[58,74,76–78]

Breast-specific glandular morphology and function are altered by exposure to environmental toxicants. Laboratory animal data demonstrate that dioxins and perfluorooctanoic acid (PFOA) interfere with maternal breast development during pregnancy and impair lactation.[30,39] Recent evidence suggests that PFOA and related chemicals also may shorten lactation or inhibit milk production in women,[31,32] similar to dichlorodiphenyl dichloroethene.[36] Breast density, a morphological factor strongly related to later breast cancer risk, has been poorly studied for environmental influences during this critical window of pregnancy.

Chemicals may alter epigenetic mechanisms to influence both transient and persistent effects on the breast. The breast undergoes a well-characterized differentiation process during pregnancy,[72,79] and exposures, such as to EDCs, during this critical window can affect breast growth and differentiation.[76] Morphological and cellular changes during pregnancy are linked to alterations in the epigenome, because chromatin structure is directly linked to development and cell fate.[79] Pregnancy-associated epigenetic signatures in the breast and other tissues persist after breast involution.[80,81] In addition, some chromatin remodeling complexes are responsive to estrogen and progesterone,[82,83] which are increased in pregnancy. Thus, during pregnancy, the breast is rewriting its epigenetic program to form new structures and complete its development.[84] Therefore, environmental contaminants, particularly during pregnancy, may act on the breast through numerous mechanisms—including endocrine disruption, alterations in chromatin structure, and cell-type-specific aberrations—to alter future risk of developing breast cancer.

Pregnancy is not only the last period of breast maturation for women but also the first developmental window for her offspring. For example, exposure to environmental chemicals during pregnancy—such as DDT, polychlorinated biphenyls, and polyfluoroalkyl and PFAS—alter breast cancer risk in perimenopausal female offspring.[33,34,37,38] Diethylstilbestrol (DES), a drug prescribed for women from 1938 to 1971 to prevent miscarriage, exemplifies how pregnancy is a susceptible time period for breast development in women and their daughters. One in six (vs. one in eight in the general population) DES-prescribed pregnant women developed breast cancer (relative risk = 1.27, 95% confidence interval [CI] = 1.07–1.52),[85] and a higher breast cancer risk in DES daughters over 40 years of age also is reported (hazard ratio = 1.82, 95% CI = 1.04–3.18),[86] among numerous other adverse health outcomes. Nongenetic risk factors, including contaminant exposures that can alter genetic and epigenetic programming to promote breast tumorigenesis, may contribute to observed racial disparities of earlier age of onset and higher rates of more aggressive breast cancer subtypes in African American women.[87]

### Subfertility, Pregnancy Complications, and Maternal Morbidity

Environmental exposures can interfere with a woman's fertility either directly, via disrupted endocrine signaling or

reproductive axis function, or indirectly, via their influence on health conditions, such as polycystic ovarian syndrome (PCOS) or uterine fibroids, that can reduce fertility and increase maternal morbidity. Subfertility can compel the use of assisted reproductive technologies (ART), which increase morbidities, including Caesarean delivery, preeclampsia, hemorrhage, HDP, gestational diabetes, placental abnormalities, thromboembolism, and maternal death.[88–92]

Links have been documented between environmental exposures and conditions that impact fertility and maternal morbidity. Air pollution, including $NO_2$ and $PM_{2.5}$, has been associated with increased risk of PCOS.[5] Uterine fibroids, benign tumors of the uterine muscle, may be influenced by environmental exposures as epidemiologic and laboratory studies indicate that EDCs and metals could play a role.[21–23,40–42] Compared to white women, African American women have earlier onset of fibroids and worse symptomatology, resulting in an increased risk of pregnancy bleeding and Caesarean delivery.[45]

Air pollution has been directly associated with reduced fertility.[6] Specifically, $NO_2$,[7] $PM_{2.5}$,[7] and metals[12,24–27] have been associated with reduced conception rates, infertility, or increased pregnancy loss. Exposure to $NO_2$ and ozone, particularly around ovulation, may reduce conception.[8] Traffic pollution has been associated with increased risk of miscarriage among nonsmokers[10] and an increased risk of infertility more broadly.[9] Subfertility caused by air pollution may lead women to ART, which is less successful for exposed women. $NO_2$ and $PM_{2.5}$ are associated with increased ART cycle failure rates.[13] Carbon monoxide[14] and $PM_{2.5}$[15] are associated with decreased conception rates. Decreased live birth rates are associated with $NO_2$,[12,15,16] $SO_2$,[17] ozone,[15] and $PM_{2.5}$.[13] An ecologic association between air pollutant peaks and monthly *in vitro* fertilization pregnancy failure rates has been observed.[11]

### Metabolic Disorders

Metabolic disorders during pregnancy can impact a woman's short-term and long-term physiology. Women with gestational diabetes have a seven-fold increase in the risk of type 2 diabetes after the gestational period and the postpartum incidence of metabolic syndrome is as high as 12%.[88,93,94] The increase in metabolic syndrome also is observed in women without gestational diabetes and is greater among women with high prepregnancy body mass index[95] or elevated diastolic blood pressure during pregnancy.[29] Unequal burden of exposure to chemicals, such as EDCs, is an underresearched contributor to the unequal burden of metabolic disease risk in Latinos, African Americans, and low-income populations.[56]

Exposure to environmental contaminants during pregnancy is implicated in metabolic changes. Repeated exposure to such EDCs as phthalates, parabens, and phenols results in dysregulated glucose metabolism/tolerance or changes in maternal thyroid hormone levels during pregnancy.[44,52,96–98] In addition, both experimental and epidemiologic evidence suggests that PFAS and certain metals are metabolic disruptors that may adversely influence cardiometabolic health, interfere with glucose control, and increase risk of hypertension and hyperlipidemia.[29,35] The impact of EDCs on thyroid function, glucose metabolism and obesity, fertility, and carcinogenesis mainly occurs through epigenetic mechanisms,[43] and their contributions to maternal metabolic issues likely impact long-term maternal health versus immediate postpartum effects.[99]

## Conclusion

Environmental exposures co-occurring in varying mixtures in the air we breathe, the food we eat, and beyond can affect maternal morbidity and mortality. Environmental health is an important component of maternal health, and observed health disparities in maternal health may be driven by elevated exposures to chemical and nonchemical stressors. In this review, we illustrate specific examples of maternal vulnerabilities to chemical exposures in pregnancy. HDP have been linked to a variety of environmental exposures, and mechanistic studies underscore the potential for such exposures to disrupt placentation and hemodynamic regulation. Breast development, particularly during the critical window of pregnancy, is sensitive to perturbation by environmental contaminants, which may contribute to impaired breastfeeding and later breast cancer risk. A variety of environmental exposures may lead to subfertility, increasing the risk of ART treatments, which are accompanied by numerous maternal health risks. Alterations during pregnancy may permanently alter metabolic and cardiovascular function.

Future research is needed addressing knowledge gaps in maternal environmental health to better understand pregnancy as a susceptible window and to understand the mechanisms underlying increased risk of disease (*e.g.*, diabetes, cardiovascular events, obesity, or breast cancer). The maternal exposome must be assessed to characterize how the milieu of chemical and nonchemical stressors we encounter throughout life can adversely impact maternal health through exposure-outcome pathways. Capturing environmental exposures across diverse racial/ethnic populations in big data initiatives, such as the All of Us Research Program, will be crucial for accelerating maternal environmental health research. Biomarkers of exposure may inform the path for personalized exposure monitoring and interventions to prevent adverse maternal health outcomes. These efforts will require collaborative science across a variety of disciplines, with the ultimate goal of disseminating research that informs policy to prevent maternal mortality and morbidity.

In sum, these few examples show the ability of prenatal environmental exposures to exert influence on maternal morbidity and mortality across the life course. By taking steps to identify and reduce exposures in this critical window, pregnant women, aided by their health care providers, can protect their own health, not just the health of their children.

Resources for more information on environmental health issues relevant to pregnant women include the following:

National Institute of Environmental Health Sciences

- https://factor.niehs.nih.gov/2020/1/papers/traffic/index.htm
- https://factor.niehs.nih.gov/2019/12/community-impact/apple/index.htm
- https://niehs.nih.gov/health/topics/population/whealth/index.cfm
- https://niehs.nih.gov/health/topics/agents/cosmetics/index.cfm

- https://niehs.nih.gov/health/materials/environmental_factors_and_breast_cancer_risk_508.pdf
- https://niehs.nih.gov/health/materials/endocrine_disruptors_508.pdf
- https://niehs.nih.gov/health/materials/flame_retardants_508.pdf
- https://niehs.nih.gov/health/materials/perfluoroalkyl_and_polyfluoroalkyl_substances_508.pdf
- https://niehs.nih.gov/health/materials/partnerships_for_environmental_public_health_peph_508.pdf

Partnerships for Environmental Public Health

- https://niehs.nih.gov/research/supported/translational/peph/resources/index.cfm

Centers for Disease Control and Prevention

- https://cdc.gov/reproductivehealth/maternalinfanthealth/pregnancy-relatedmortality.htm
- https://cdc.gov/reproductivehealth/maternalinfanthealth/severematernalmorbidity.html
- https://cdc.gov/mmwr/volumes/68/wr/mm6835a3.htm?s_cid=mm6835a3_w
- https://cdc.gov/vitalsigns/maternal-deaths/
- https://cdc.gov/mmwr/volumes/68/wr/mm6818e1.htm?s_cid=mm6818e1_w

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### References

1. Centers for Disease Control and Prevention. National report on human exposure to environmental chemicals, updated tables, January 2019. Available at: https://cdc.gov/exposurereport/index.html Accessed June 17, 2020.
2. James-Todd TM, Chiu YH, Zota AR. Racial/ethnic disparities in environmental endocrine disrupting chemicals and women's reproductive health outcomes: Epidemiological examples across the life course. Curr Epidemiol Rep 2016;3:161–180.
3. National Toxicology Program (NTP). NTP monograph on the systematic review of traffic-related air pollution and hypertensive disorders of pregnancy. NTP Monograph 7. Research Triangle Park, NC: National Toxicology Program, 2019. Available at: https://ntp.niehs.nih.gov/ntp/ohat/trap/mgraph/trap_final_508.pdf Accessed June 17, 2020.
4. Pedersen M, Stayner L, Slama R, et al. Ambient air pollution and pregnancy-induced hypertensive disorders: A systematic review and meta-analysis. Hypertension 2014;64:494–500.
5. Lin SY, Yang YC, Chang CY, et al. Risk of polycystic ovary syndrome in women exposed to fine air pollutants and acidic gases: A nationwide cohort analysis. Int J Environ Res Public Health 2019;16:4816.
6. Conforti A, Mascia M, Cioffi G, et al. Air pollution and female fertility: A systematic review of literature. Reprod Biol Endocrinol 2018;16:117.
7. Slama R, Bottagisi S, Solansky I, Lepeule J, Giorgis-Allemand L, Sram R. Short-term impact of atmospheric pollution on fecundability. Epidemiology 2013;24:871–879.
8. Nobles CJ, Schisterman EF, Ha S, Buck Louis GM, Sherman S, Mendola P. Time-varying cycle average and daily variation in ambient air pollution and fecundability. Hum Reprod 2018;33:166–176.
9. Mahalingaiah S, Hart JE, Laden F, et al. Adult air pollution exposure and risk of infertility in the Nurses' Health Study II. Hum Reprod 2016;31:638–647.
10. Green RS, Malig B, Windham GC, Fenster L, Ostro B, Swan S. Residential exposure to traffic and spontaneous abortion. Environ Health Perspect 2009;117:1939–1944.
11. Kang J, Lee JY, Song H, Shin SJ, Kim J. Association between in vitro fertilization success rate and ambient air pollution: A possible explanation of within-year variation of in vitro fertilization success rate. Obstet Gynecol Sci 2020;63:72–79.
12. Quraishi SM, Lin PC, Richter KS, et al. Ambient air pollution exposure and fecundability in women undergoing in vitro fertilization. Environ Epidemiol 2019;3:e036.
13. Gaskins AJ, Fong KC, Abu Awad Y, et al. Time-varying exposure to air pollution and outcomes of in vitro fertilization among couples from a fertility clinic. Environ Health Perspect 2019;127:77002.
14. Choe SA, Jun YB, Lee WS, Yoon TK, Kim SY. Association between ambient air pollution and pregnancy rate in women who underwent IVF. Hum Reprod 2018;33:1071–1078.
15. Legro RS, Sauer MV, Mottla GL, et al. Effect of air quality on assisted human reproduction. Hum Reprod 2010;25:1317–1324.
16. Gaskins AJ, Mínguez-Alarcón L, Fong KC, et al. Supplemental folate and the relationship between traffic-related air pollution and livebirth among women undergoing assisted reproduction. Am J Epidemiol 2019;188:1595–1604.
17. Wang X, Cai J, Liu L, et al. Association between outdoor air pollution during in vitro culture and the outcomes of frozen-thawed embryo transfer. Hum Reprod 2019;34:441–451.
18. Rosen EM, Muñoz MI, McElrath T, Cantonwine DE, Ferguson KK. Environmental contaminants and preeclampsia: A systematic literature review. J Toxicol Environ Health B Crit Rev 2018;21:291–319.
19. Poropat AE, Laidlaw MAS, Lanphear B, Ball A, Mielke HW. Blood lead and preeclampsia: A meta-analysis and review of implications. Environ Res 2018;160:12–19.
20. Liu B, Lehmler HJ, Sun Y, et al. Association of bisphenol A and its substitutes, bisphenol F and bisphenol S, with obesity in United States children and adolescents. Diabetes Metab J 2019;43:59–75.
21. Johnstone EB, Louis GM, Parsons PJ, et al. Increased urinary cobalt and whole blood concentrations of cadmium and lead in women with uterine leiomyomata: Findings from the ENDO Study. Reprod Toxicol 2014;49:27–32.
22. Ye S, Chung HW, Jeong K, et al. Blood cadmium and volume of uterine fibroids in premenopausal women. Ann Occup Environ Med 2017;29:22.

23. Gao X, Yu L, Moore AB, Kissling GE, Waalkes MP, Dixon D. Cadmium and proliferation in human uterine leiomyoma cells: Evidence of a role for EGFR/MAPK pathways but not classical estrogen receptor pathways. Environ Health Perspect 2015;123:331–336.
24. Cole DC, Wainman B, Sanin LH, Weber JP, Muggah H, Ibrahim S. Environmental contaminant levels and fecundability among non-smoking couples. Reprod Toxicol 2006; 22:13–19.
25. Rahman SN, Fatima P, Chowdhury AQ, Rahman MW. Blood level of lead in women with unexplained infertility. Mymensingh Med J 2013;22:508–512.
26. Buck Louis GM. Persistent environmental pollutants and couple fecundity: An overview. Reproduction 2014;147: R97–R104.
27. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, Farias P, Rios C, Blanco J. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol 1999;150:590–597.
28. Quansah R, Armah FA, Essumang DK, et al. Association of arsenic with adverse pregnancy outcomes/infant mortality: A systematic review and meta-analysis. Environ Health Perspect 2015;123:412–421.
29. Farzan SF, Brickley EB, Li Z, et al. Maternal and infant inflammatory markers in relation to prenatal arsenic exposure in a U.S. pregnancy cohort. Environ Res 2017;156: 426–433.
30. White SS, Calafat AM, Kuklenyik Z, et al. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. Toxicol Sci 2007;96:133–144.
31. Timmermann CAG, Budtz-Jorgensen E, Petersen MS, et al. Shorter duration of breastfeeding at elevated exposures to perfluoroalkyl substances. Reprod Toxicol 2017;68:164–170.
32. Romano ME, Xu Y, Calafat AM, et al. Maternal serum perfluoroalkyl substances during pregnancy and duration of breastfeeding. Environ Res 2016;149:239–246.
33. Cohn BA, La Merrill MA, Krigbaum NY, et al. In utero exposure to poly- and perfluoroalkyl substances (PFASs) and subsequent breast cancer. Reprod Toxicol 2020;92: 112–119.
34. Bonefeld-Jorgensen EC, Long M, Fredslund SO, Bossi R, Olsen J. Breast cancer risk after exposure to perfluorinated compounds in Danish women: A case-control study nested in the Danish National Birth Cohort. Cancer Causes Control 2014;25:1439–1448.
35. Barry V, Darrow LA, Klein M, Winquist A, Steenland K. Early life perfluorooctanoic acid (PFOA) exposure and overweight and obesity risk in adulthood in a community with elevated exposure. Environ Res 2014;132:62–69.
36. Rogan WJ, Gladen BC, McKinney JD, et al. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects on growth, morbidity, and duration of lactation. Am J Public Health 1987;77:1294–1297.
37. Cohn BA, Cirillo PM, Terry MB. DDT and breast cancer: Prospective study of induction time and susceptibility windows. J Natl Cancer Inst 2019;111:803–810.
38. Cohn BA, Terry MB, Plumb M, Cirillo PM. Exposure to polychlorinated biphenyl (PCB) congeners measured shortly after giving birth and subsequent risk of maternal breast cancer before age 50. Breast Cancer Res Treat 2012; 136:267–275.
39. Fenton SE, Hamm JT, Birnbaum LS, Youngblood GL. Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Sci 2002;67: 63–74.
40. Zota AR, Geller RJ, Calafat AM, Marfori CQ, Baccarelli AA, Moawad GN. Phthalates exposure and uterine fibroid burden among women undergoing surgical treatment for fibroids: A preliminary study. Fertil Steril 2019;111:112–121.
41. Yu L, Das P, Vall AJ, et al. Bisphenol A induces human uterine leiomyoma cell proliferation through membrane-associated ERα36 via nongenomic signaling pathways. Mol Cell Endocrinol 2019;484:59–68.
42. Trabert B, Chen Z, Kannan K, et al. Persistent organic pollutants (POPs) and fibroids: Results from the ENDO study. J Expo Sci Environ Epidemiol 2015;25:278–285.
43. Street ME, Angelini S, Bernasconi S, et al. Current knowledge on endocrine disrupting chemicals (EDCs) from animal biology to humans, from pregnancy to adulthood: Highlights from a national Italian meeting. Int J Mol Sci 2018;19:1647.
44. Gaston SA, Birnbaum LS, Jackson CL. Synthetic chemicals and cardiometabolic health across the life course among vulnerable populations: A review of the literature from 2018 to 2019. Curr Environ Health Rep 2020;7:30–47.
45. Laughlin-Tommaso SK, Jacoby VL, Myers ER. Disparities in fibroid incidence, prognosis, and management. Obstet Gynecol Clin North Am 2017;44:81–94.
46. Duran DG, Pérez-Stable EJ. Novel approaches to advance minority health and health disparities research. Am J Public Health 2019;109:S8–S10.
47. Williams DR, Collins C. Racial residential segregation: A fundamental cause of racial disparities in health. Public Health Rep 2001;116:404–416.
48. Jones CP. Levels of racism: A theoretic framework and a gardener's tale. Am J Public Health 2000;90:1212–1215.
49. Feinstein L, McWhorter KL, Gaston SA, Troxel WM, Sharkey KM, Jackson CL. Racial/ethnic disparities in sleep duration and sleep disturbances among pregnant and nonpregnant women in the United States. J Sleep Res 2020;29: e13000.
50. James-Todd T, Terry MB, Rich-Edwards J, Deierlein A, Senie R. Childhood hair product use and earlier age at menarche in a racially diverse study population: A pilot study. Ann Epidemiol 2011;21:461–465.
51. McDonald JA, Tehranifar P, Flom JD, Terry MB, James-Todd T. Hair product use, age at menarche and mammographic breast density in multiethnic urban women. Environ Health 2018;17:1.
52. Noor N, Ferguson KK, Meeker JD, et al. Pregnancy phthalate metabolite concentrations and infant birth weight by gradations of maternal glucose tolerance. Int J Hyg Environ Health 2019;222:395–401.
53. Polinski KJ, Dabelea D, Hamman RF, et al. Distribution and predictors of urinary concentrations of phthalate metabolites and phenols among pregnant women in the Healthy Start Study. Environ Res 2018;162:308–317.
54. Verstraete SG, Wojcicki JM, Perito ER, Rosenthal P. Bisphenol A increases risk for presumed non-alcoholic fatty liver disease in Hispanic adolescents in NHANES 2003–2010. Environ Health 2018;17:12.
55. Wenzel AG, Brock JW, Cruze L, et al. Prevalence and predictors of phthalate exposure in pregnant women in Charleston, SC. Chemosphere 2018;193:394–402.

56. Ruiz D, Becerra M, Jagai JS, Ard K, Sargis RM. Disparities in environmental exposures to endocrine-disrupting chemicals and diabetes risk in vulnerable populations. Diabetes Care 2018;41:193–205.
57. Zota AR, Shamasunder B. The environmental injustice of beauty: Framing chemical exposures from beauty products as a health disparities concern. Am J Obstet Gynecol 2017; 217:418.e1–418.e6.
58. Varshavsky J, Smith A, Wang A, et al. Heightened susceptibility: A review of how pregnancy and chemical exposures influence maternal health. Reprod Toxicol 2019; 92:14–56.
59. Johnson GS, Rainey SA, Johnson LS. Dickson, Tennessee and toxic wells: An environmental racism case study. Race Gend Class 2008;15:204–223.
60. ACOG practice bulletin no. 202: Gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:e1–e25.
61. Craici I, Wagner S, Garovic VD. Preeclampsia and future cardiovascular risk: Formal risk factor or failed stress test? Ther Adv Cardiovasc Dis 2008;2:249–259.
62. Williams D. Long-term complications of preeclampsia. Semin Nephrol 2011;31:111–122.
63. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. BMJ 2016;353:i1753.
64. Eskenazi B, Bracken MB, Holford TR, Grady J. Exposure to organic solvents and hypertensive disorders of pregnancy. Am J Ind Med 1988;14:177–188.
65. Gao F, Hu W, Li Y, Shen H, Hu J. Mono-2-ethylhexyl phthalate inhibits human extravillous trophoblast invasion via the PPAR$\gamma$ pathway. Toxicol Appl Pharmacol 2017; 327:23–29.
66. Morice L, Benaîtreau D, Dieudonné MN, et al. Antiproliferative and proapoptotic effects of bisphenol A on human trophoblastic JEG-3 cells. Reprod Toxicol 2011;32: 69–76.
67. Adibi JJ, Hauser R, Williams PL, et al. Placental biomarkers of phthalate effects on mRNA transcription: Application in epidemiologic research. Environ Health 2009;8:20.
68. Ferguson KK, McElrath TF, Cantonwine DE, Mukherjee B, Meeker JD. Phthalate metabolites and bisphenol-A in association with circulating angiogenic biomarkers across pregnancy. Placenta 2015;36:699–703.
69. Li Q, Kappil MA, Li A, et al. Exploring the associations between microRNA expression profiles and environmental pollutants in human placenta from the National Children's Study (NCS). Epigenetics 2015;10:793–802.
70. Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. J Am Soc Hypertens 2009;3:332–350.
71. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol 2017;232:R27–R44.
72. Russo J, Russo IH. Development of the human breast. Maturitas 2004;49:2–15.
73. Keen CL, Taubeneck MW, Zidenberg-Cherr S, Daston GP, Rogers JM. Toxicant exposure and trace element metabolism in pregnancy. Environ Toxicol Pharmacol 1997;4: 301–308.
74. Terry MB, Michels KB, Brody JG, et al. Environmental exposures during windows of susceptibility for breast cancer: A framework for prevention research. Breast Cancer Res 2019;21:96.
75. Kumar P, Magon N. Hormones in pregnancy. Niger Med J 2012;53:179–183.
76. Fenton SE. Endocrine-disrupting compounds and mammary gland development: Early exposure and later life consequences. Endocrinology 2006;147:S18–S24.
77. Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC). Breast cancer and the environment: Prioritizing prevention. Report of the interagency breast cancer and environmental research coordinating committee, 2013. Available at: https://niehs.nih.gov/about/assets/docs/breast_cancer_and_the_environment_prioritizing_prevention_508.pdf Accessed June 18, 2020.
78. Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. Environmental exposures and mammary gland development: State of the science, public health implications, and research recommendations. Environ Health Perspect 2011;119:1053–1061.
79. Ginger MR, Rosen JM. Pregnancy-induced changes in cell-fate in the mammary gland. Breast Cancer Res 2003;5:192–197.
80. Russo J, Santucci-Pereira J, de Cicco RL, et al. Pregnancy-induced chromatin remodeling in the breast of postmenopausal women. Int J Cancer 2012;131:1059–1070.
81. Katz TA, Liao SG, Palmieri VJ, et al. Targeted DNA methylation screen in the mouse mammary genome reveals a parity-induced hypermethylation of Igf1r that persists long after parturition. Cancer Prev Res (Phila) 2015;8: 1000–1009.
82. Mymryk JS, Archer TK. Dissection of progesterone receptor-mediated chromatin remodeling and transcriptional activation in vivo. Genes Dev 1995;9:1366–1376.
83. Mohammed H, Russell IA, Stark R, et al. Progesterone receptor modulates ERalpha action in breast cancer. Nature 2015;523:313–317.
84. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis 2018;5:77–106.
85. Titus-Ernstoff L, Hatch EE, Hoover RN, et al. Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. Br J Cancer 2001;84:126–133.
86. Hoover R, Fraumeni JF, Everson R, Myers MH. Cancer of the uterine corpus after hormonal treatment for breast cancer. Lancet 1976;1:885–887.
87. Wright N, Akinyemiju T, Subhedar P, Rida P, Aneja R. Targeting risk factors for reducing the racially disparate burden in breast cancer. Front Biosci (Schol Ed) 2019;11: 136–160.
88. Lei Q, Zhou X, Zhou YH, et al. Prehypertension during normotensive pregnancy and postpartum clustering of cardiometabolic risk factors: A prospective cohort study. Hypertension 2016;68:455–463.
89. Nyfløt LT, Sandven I, Stray-Pedersen B, et al. Risk factors for severe postpartum hemorrhage: A case-control study. BMC Pregnancy Childbirth 2017;17:17.
90. Qin J, Liu X, Sheng X, Wang H, Gao S. Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: A meta-analysis of cohort studies. Fertil Steril 2016;105:73–85.e1–e6.
91. Vloeberghs V, Peeraer K, Pexsters A, D'Hooghe T. Ovarian hyperstimulation syndrome and complications of ART. Best Pract Res Clin Obstet Gynaecol 2009;23:691–709.

92. Dayan N, Joseph KS, Fell DB, et al. Infertility treatment and risk of severe maternal morbidity: A propensity score-matched cohort study. CMAJ 2019;191:E118–E127.
93. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. Lancet 2009;373:1773–1779.
94. Gunderson EP, Jacobs DR, Jr., Chiang V, et al. Childbearing is associated with higher incidence of the metabolic syndrome among women of reproductive age controlling for measurements before pregnancy: The CARDIA study. Am J Obstet Gynecol 2009;201:177.e1–e9.
95. Gunderson EP, Murtaugh MA, Lewis CE, Quesenberry CP, West DS, Sidney S. Excess gains in weight and waist circumference associated with childbearing: The Coronary Artery Risk Development in Young Adults Study (CARDIA). Int J Obes Relat Metab Disord 2004;28:525–535.
96. Aker AM, Johns L, McElrath TF, Cantonwine DE, Mukherjee B, Meeker JD. Associations between maternal phenol and paraben urinary biomarkers and maternal hormones during pregnancy: A repeated measures study. Environ Int 2018;113:341–349.
97. Arbuckle TE, Weiss L, Fisher M, et al. Maternal and infant exposure to environmental phenols as measured in multiple biological matrices. Sci Total Environ 2015;508:575–584.
98. Mitro SD, Johnson T, Zota AR. Cumulative chemical exposures during pregnancy and early development. Curr Environ Health Rep 2015;2:367–378.
99. Planchart A, Green A, Hoyo C, Mattingly CJ. Heavy metal exposure and metabolic syndrome: Evidence from human and model system studies. Curr Environ Health Rep 2018;5:110–124.

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