

Maternal Smoking During Pregnancy and Offspring Health Outcomes: The Role of Epigenetic Research in Informing Legal Policy and Practice

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Scientific advances in epidemiology and epigenetics emphasize the importance of prenatal and intergenerational environmental influences and epigenetic regulation in altering vulnerability for later health outcomes. These findings may have wide-ranging legal implications; however, to avoid misapplication, a thorough understanding of the scientific literature and legal precedent is warranted. A growing body of literature suggests that negative health outcomes associated with prenatal smoke exposure may result, in part, from aberrant epigenetic regulation of gene expression. Such findings emphasize the need to reduce rates of prenatal cigarette smoke exposure in order to promote health for both current and future generations. This Article provides a focused overview of research examining the interrelationships between maternal smoking during pregnancy, epigenetic regulation, and vulnerability for later health outcomes. Additionally, this Article discusses legal, ethical, and policy challenges related to reducing smoke exposure during pregnancy.

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INTRODUCTION

One's prenatal environment, and in some cases the prenatal environment of one's ancestors, may contribute to the development of cardiovascular disease, type 2 diabetes, obesity, cancer, and neurodevelopmental disorders.¹ Recent advances in epidemiological theory² and epigenetics³ have led to a major paradigm shift in research investigating the causes of later health and behavior. These advances provide a useful framework and novel tools to help examine how early environmental influences impact vulnerability for later health outcomes.

Many of society's most costly,⁴ impairing, and deadly diseases⁵ have early developmental origins.⁶ From a public health perspective, these findings hold great promise as preventative interventions may aim to reduce exposure to adverse environmental influences. Furthermore, there has been increased interest in understanding the processes linking early environments—even those from previous generations—to later health outcomes. Epigenetic mechanisms may provide a bridge for how the environment gets “under the skin” and impacts biological vulnerability to future diseases and complications. Future health interventions may also target modifiable epigenetic mechanisms.⁷

In addition to public health implications, the role of early environmental influences and related epigenetic mechanisms on later health challenges may have wide-ranging implications for legal policy and practice. A growing body of literature suggests that negative health outcomes associated with prenatal smoke exposure may result partially from aberrant epigenetic regulation of gene expression. Furthermore, intergenerational epigenetic effects may transmit the adverse effects of

1. See Tessa Roseboom et al., *The Dutch Famine and its Long-Term Consequences for Adult Health*, 82 EARLY HUM. DEV. 485, 486 (2006).

2. Epidemiological theory, such as the “developmental origins of health and disease” hypothesis, provides a framework for understanding the causes and patterns of disease. See generally Peter D. Gluckman & Mark A. Hanson, *Living with the Past: Evolution, Development, and Patterns of Disease*, 305 SCIENCE 1733 (2004).

3. Epigenetics researches changes in gene expression that are not caused by changes in the sequence of DNA. See generally Adrian Bird, *Perceptions of Epigenetics*, 447 NATURE 396 (2007).

4. See generally Benjamin G. Druss et al., *The Most Expensive Medical Conditions In America*, 21 HEALTH AFF., no. 4, 2002, at 105.

5. See ARIALDI M. MININO & BETTY L. SMITH, CTRS. FOR DISEASE CONTROL & PREVENTION, 49 NATIONAL VITAL STATISTICS REPORTS 12, at 2–4 (Oct. 2001) (discussing the leading causes of death from 1999–2000, including diseases).

6. See generally Robert Barouki et al., *Developmental Origins of Non-Communicable Disease: Implications for Research and Public Health*, ENVIRONMENTAL HEALTH (Jun. 27, 2012, 11:42 AM), <http://www.ehjournal.net/content/11/1/42>.

7. See *infra* Part I.B.3.

cigarette smoke exposure from one generation to the next.⁸ If aberrant epigenetic effects are found to link environmental exposure with negative health outcomes, then epigenetic evidence may be considered when determining criminal culpability or negligence of the “bad actor” who has exposed others to cigarette smoke. In addition, given that smoking-associated negative health outcomes may be realized in subsequent generations through epigenetic transmission, problems may also arise in applying statutes of limitation to such cases. Consider these examples of potential cases:

If a grandmother smoked during her pregnancy with a daughter, should that grandmother be held responsible for smoking-associated diseases and symptoms present in her grandchild—even if that grandchild’s only exposure to cigarette smoke resulted from her mother’s prenatal exposure to smoke?

The literature on the potential hazards of passive (or “secondhand”) smoke has grown substantially. Due to this growing awareness, might a father who smoked near a pregnant woman be held liable for negative smoking-related health consequences that result from the many chemicals now known to be present in secondhand smoke? Given that even small doses of harmful exposures can lead to deleterious effects, what level of cigarette smoke exposure would be considered prosecutable?

This Article highlights the potential ethical, legal, and policy issues stemming from research on the developmental origins of later health outcomes. Part I provides background and an overview of the Developmental Origins of Health and Disease model, with an emphasis on fetal programming. Part II discusses epigenetic concepts within the context of environmental epigenetics and reviews the impact of smoke exposure in utero on epigenetic processes and health outcomes. The Article concludes, in Part III, with a discussion of ethical, legal, and policy implications of the interpretation and application of epigenetic findings.

I. FETAL ORIGINS OF LATER HEALTH OUTCOMES

A. BARKER’S HYPOTHESIS AND THE DUTCH FAMINE OF 1944–1945

Multiple epidemiological studies have observed that populations exposed to a limited nutrient supply in utero and who experienced restricted fetal growth are at greater risk for diseases later in life.⁹ Barker’s Hypothesis, which stems from these observations, states that fetal

8. See generally Dawn P. Misra et al., *Maternal Smoking and Birth Weight: Interaction with Parity and Mother’s Own In Utero Exposure to Smoking*, 16 EPIDEMIOLOGY 288 (2005).

9. See, e.g., D.J.P. Barker, *The Origins of the Developmental Origins Theory*, 261 J. INTERNAL MED. 412 (2007); Pathik D. Wadhwa et al., *Developmental Origins of Health and Disease: Brief History of the Approach and Current Focus on Epigenetic Mechanisms*, 27 SEMINARS REPROD. MED. 358 (2009).

undernourishment leads to lasting alterations in the structure and function of organs and subsequent increased vulnerability for adult disease.¹⁰ In particular, the Dutch Famine Birth Cohort study¹¹ has offered key, but tragic, insights into the association of fetal malnutrition with later health.

In support of the Allied Forces' momentum during World War II, the exiled Dutch government called for a strike of the national railroads.¹² In response, the German administration placed a food transport embargo on the western Netherlands, which was still under German control.¹³ The embargo was altered in November 1944 to allow food transport by water, but due to an early and harsh winter, this form of transport was not feasible.¹⁴ The embargo and harsh winter led to famine in the western Netherlands, and as a result, adult daily rations dropped to between 400–800 calories from December 1944 to April 1945, and supplementary calories for women who were pregnant or nursing were no longer available.¹⁵

The Dutch Famine (or Hunger Winter) was associated with significant morbidity and mortality. The link between in utero environment and later health outcomes was illuminated by historical circumstances such as the circumscribed period of the famine, detailed records of daily rations and health outcomes and limited supply of supplemental food. The Dutch Famine Birth Cohort Study followed individuals who were exposed to the famine prenatally and assessed associations of prenatal malnutrition with later health outcomes. Results from this study demonstrated that fetal malnutrition was associated with increased risk for various non-communicable health and neurodevelopmental problems including cardiovascular disease,¹⁶ type 2 diabetes,¹⁷ cancer,¹⁸ obesity,¹⁹ and schizophrenia.²⁰ The relationship between fetal malnutrition and later health outcomes also depended on the gestational timing of famine.²¹ These findings emphasize the critical importance of environmental influences during prenatal development and

10. Barker, *supra* note 9, at 412.

11. Roseboom et al., *Effects of Prenatal Exposure to the Dutch Famine on Adult Disease in Later Life: An Overview*, 185 *MOLECULAR & CELLULAR ENDOCRINOLOGY* 93 (2001).

12. *Id.* at 94.

13. *Id.*

14. *Id.*

15. *Id.*

16. Rosenbloom et al., *supra* note 1, at 489.

17. *Id.* at 487–88.

18. *Id.* at 489.

19. See generally Gian-Paolo Ravelli et al., *Obesity in Young Men After Famine Exposure In Utero and Early Infancy*, 295 *NEW ENG. J. MED.* 349 (1976).

20. See generally E.S. SUSSER & S.P. LIN, *Schizophrenia After Prenatal Exposure to the Dutch Hunger Winter of 1944–1945*, 49 *ARCHIVES GEN. PSYCHIATRY* 983 (1992).

21. Rosenbloom et al., *supra* note 1, at 488.

that vulnerability for a specified health outcome may relate to both the timing and nature of prenatal environmental exposures.

B. THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE HYPOTHESIS

Findings from the Dutch Famine Birth Cohort study emphasize the critical importance of the prenatal period in the programming of multiple developmental systems. Other studies of humans and animals have broadened our understanding of adverse prenatal environmental influences and their relationship to later health outcomes. Such studies have shown, for example, that exposure to toxicants (such as cigarette smoke), maternal illnesses (such as influenza or depression), medications (such as antidepressants), fetal hypoxia, and other pregnancy complications have an adverse impact on later health.²² To account for these findings, Barker's hypothesis was expanded to the Developmental Origins of Health and Disease hypothesis ("DOHaD").²³

DOHaD provides a comprehensive framework to conceptualize how the interplay of genetic and early environmental factors can cause vulnerability for later health, behavior, and disease. DOHaD hypothesizes that prenatal environmental influences contribute to the programming of the fetus and, in a way, attempt to impart a maternal forecast on the developing fetus. The theory of "fetal programming"²⁴ postulates that a large milieu of exposures comprise the prenatal environment, including nutrients, drugs, trauma, and stress. A prenatal environment comprised mostly of healthy exposures and proper nutrition and devoid of negative exposures is theorized to result in the mother imparting a rich maternal forecast on her fetus—a prediction that the postnatal environment will be one in which resources are plentiful and harmful negative exposures are minimal.²⁵ On the contrary, a largely adverse prenatal environment (one comprised of a number of negative exposures and mostly devoid of positive environmental influences) is theorized to result in a mother imparting a poor maternal forecast on her fetus, which is often characterized by restricted fetal growth.²⁶ This negative maternal forecast predicts that the postnatal environment will be one in which positive resources and exposures are scarce while

22. See, e.g., K. Latimer et al., *Disruptive Behaviour Disorders: A Systematic Review of Environmental Antenatal and Early Years Risk Factors*, 38 *CHILD: CARE, HEALTH & DEV.* 609, 611–28 (2012).

23. See generally Gluckman & Hanson, *supra* note 2.

24. Valerie S. Knopik et al., *The Epigenetics of Maternal Cigarette Smoking During Pregnancy and Effects on Child Development*, 24 *DEV. & PSYCHOPATHOLOGY* 1377, 1379 (2012).

25. *Id.*

26. See generally C.N. Hales & D.J.P. Barker, *Type 2 (Non-Insulin-Dependent) Diabetes Mellitus: the Thrifty Phenotype Hypothesis*, 35 *DIABETOLOGIA* 595 (1992). According to Hales and Barker the "thrifty phenotype" describes the notion that fetal malnutrition is associated with restricted fetal growth and lasting changes in glucose-insulin metabolism which increases vulnerability for metabolic problems, including type 2 diabetes, when exposed to a nutrient rich postnatal environment. See generally *id.*

negative exposures are abundant. Moreover, maternal forecasts that are discordant with the post-birth environment—that incorrectly predict the post-birth environment—have been hypothesized to be associated with a number of negative consequences for the child later in life, such as an increased risk for cardiovascular and metabolic diseases. This outcome was observed in many of the children exposed to in utero famine during the Dutch Hunger Winter, who were imparted with negative maternal forecasts and were born growth-restricted but who experienced a post-birth environment that was abundant with resources.²⁷

Increased vulnerability for poor health outcomes may result from multiple developmental processes including, but not limited to, predictive adaptive responses, developmental delays, or developmental disruptions. Predictive adaptive responses describe an organism's prenatal structural and functional adaptations to promote survival in a similar postnatal environment.²⁸ Vulnerability for poor health outcomes may then arise from a mismatch between the prenatal and postnatal environment. This mismatch confers vulnerability for disease as the organism is functioning in an environment for which it did not prepare. As a result, the fetus may be ill-equipped to function adaptively in the postnatal environment. For example, in response to a decreased placental-fetal blood flow, a fetus may preferentially direct blood flow and nutrients to the brain, known as the "brain-sparing effect."²⁹ Although this may promote neurovascular functioning in a nutrient poor environment, it may also constrain cerebral vascular plasticity later in life.³⁰

In addition, brain-sparing blood flow does not completely protect against later behavioral problems³¹ as the nutrient and oxygen availability is more abundant in the postnatal environment. Prenatal environmental influences may also cause vulnerability for later health problems by disrupting developmental processes. For example, exposure to teratogens, including several compounds in cigarette smoke,³² may disrupt developmental processes without any forecasted or actual adaptive advantage. Although prenatal environmental influences may directly

27. See Knopik, *supra* note 24, at 1379; see also David J.P. Barker & Phillipa M. Clark, *Fetal Undernutrition and Disease in Later Life*, 2 REVS. REPROD. 105, 109 (1997); Susanne R. de Rooij et al., *Prenatal Undernutrition and Cognitive Function in Late Adulthood*, 107 PROCEEDINGS NAT'L ACAD. SCI. U.S. 16881, 16883 (2010).

28. See generally Gluckman & Hanson, *supra* note 2. Predictive adapted responses describe the process of fetal programming in response to the prenatal milieu. *Id.*

29. Ahmet A. Baschat, *Fetal Responses to Placental Insufficiency: An Update*, 111 BJOG: INT'L J. OBSTETRICS & GYNAECOLOGY 1031, 1035 (2004).

30. Jing Fu & Per Olofsson, *Restrained Cerebral Hyperperfusion in Response to Superimposed Acute Hypoxemia in Growth-Restricted Human Fetuses with Established Brain-Sparing Blood Flow*, 82 EARLY HUM. DEV. 211, 215 (2006).

31. Sabine J. Roza et al., *What Is Spared by Fetal Brain-Sparing? Fetal Circulatory Redistribution and Behavioral Problems in the General Population*, 168 AM. J. EPIDEMIOLOGY 1145, 1145 (2008).

32. See generally Knopik, *supra* note 24.

impact vulnerability for later health outcomes, it is important to consider indirect effects and the role of other factors. Among individuals exposed to adverse prenatal environmental influences, vulnerability for later health outcomes may then be moderated by the postnatal environment and genetic effects.

1. Postnatal Environmental Influences

The postnatal environment continues to impact vulnerability for health outcomes throughout life. For example, rat pups that are exposed to low levels of maternal nurturing behavior (such as licking, grooming, and arched back nursing) exhibit increased fearful behavior and hypothalamic-pituitary-adrenal axis response to stress compared to pups exposed to high levels of maternal nurturing behavior.³³ This postnatal environmental effect is believed to be mediated, in part, by differences in DNA methylation of the glucocorticoid receptor gene in the hippocampus—an epigenetic mechanism described in detail in Part I.B.3.³⁴ Although preliminary, findings in studies of humans suggest that maternal nurturing behavior like infant stroking may produce similar behavioral outcomes.³⁵ The mechanism underlying this relationship in humans has not yet been fully examined but these findings demonstrate that postnatal environmental experiences may also impact vulnerability for later health outcomes.

2. Intergenerational Transmission of Environmental Effects

Environmental influences may also impact health outcomes in subsequent generations. For example, prenatal cigarette smoke exposure may put offspring at risk for poor health outcomes (such as low birth weight) and this relationship has been shown to be exacerbated in mothers who themselves were exposed to maternal smoking during their own fetal development.³⁶ These findings suggest that environmental exposures may have a multi-generational impact on health outcomes, which emphasizes the public health significance of limiting exposure to adverse environmental factors.³⁷

33. Ian C.G. Weaver et al., *Epigenetic Programming by Maternal Behavior*, 7 NATURE NEUROSCIENCE 847, 847 (2004).

34. *Id.*

35. Helen Sharp et al., *Frequency of Infant Stroking Reported by Mothers Moderates the Effect of Prenatal Depression on Infant Behavioural and Physiological Outcomes*, PLoS ONE, Oct. 2012, at 1, 8.

36. Misra, *supra* note 8, at 291–92.

37. Peter D. Gluckman et al., *Developmental Origins of Health and Disease: Reducing the Burden of Chronic Disease in the Next Generation*, GENOME MED. (Feb. 24, 2010, 2:14 PM), <http://www.genomemedicine.com/content/2/2/14>.

3. Genetic Influences

Most health and behavioral outcomes are multifactorial in nature, which means that across individuals, an outcome of interest (such as antisocial behavior) is influenced by many different genes and many different environmental factors. This does not, however, preclude the possibility that some individuals may have a much simpler etiology (such as rare genetic variation). Before describing the role of epigenetic effects within DOHaD, it is first necessary to provide a brief overview of how genetic variation is associated with health outcomes.

a. Direct Genetic Effects

Variation in DNA sequence or chromosomal abnormalities may directly influence vulnerability for later health outcomes. For example, although environmental factors account for the majority of variability in fetal growth,³⁸ genetic effects play a substantial role.³⁹ This example highlights the importance of considering the impact of both genetic and environmental influences factors on fetal growth (used by many research groups as a proxy measure for the quality of the in utero environment) and later health outcomes.⁴⁰

b. Gene-Environment Correlation

Although exposure to other risk factors, such as cigarette smoke, are categorized as *environmental* in nature, most environmental risk factors are correlated with genetic influences.⁴¹ Gene-environment correlation takes multiple forms,⁴² and passive gene-environment correlation may be most influential during fetal development. Passive gene-environment correlation occurs when the child's genotype, which is inherited from parents, is associated with the environment in which the child is raised.⁴³ For example, mothers may have a genetic liability to engage in risky behavior and pass down this genetic liability to their offspring. However, having a genetic liability for risky behavior also makes it more likely that the developing fetus is exposed to adverse prenatal exposures that are

38. Christina M. Hultman et al., *Birth Weight and Attention-Deficit/Hyperactivity Symptoms in Childhood and Early Adolescence: A Prospective Swedish Twin Study*, 46 J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY 370, 375 (2007).

39. *Id.*; D.O. Mook-Kanamori, *Heritability Estimates of Body Size in Fetal Life and Early Childhood*, PLoS ONE, July 2013, at 3–7.

40. See generally Valerie S. Knopik, *Maternal Smoking During Pregnancy and Child Outcomes: Real or Spurious Effect?*, 34 DEVELOPMENTAL NEUROPSYCHOLOGY 1 (2009).

41. See generally Kenneth S. Kendler & Jessica H. Baker, *Genetic Influences on Measures of the Environment: A Systematic Review*, 37 PSYCHOL. MED. 615 (2007).

42. Sara R. Jaffee & Thomas S. Price, *The Implications of Genotype–Environment Correlation for Establishing Causal Processes in Psychopathology*, 24 DEV. & PSYCHOPATHOLOGY 1253, 1253–54 (2012).

43. *Id.* at 1253.

associated with maternal risky behavior, such smoking cigarettes. Thus, it is important to disentangle the effects of a genetic liability for risky behavior and smoke exposure on later health outcomes by using genetically-informed designs. For example, comparing siblings with the same mother who were differentially exposed to prenatal smoking parses out a genetic liability for risky behavior from maternal smoking during pregnancy.⁴⁴ This genetically informed design would allow for a more focused investigation of the effect that maternal smoking during pregnancy has on later health outcomes.⁴⁵

c. *Gene-Environment Interaction*

Gene-environment interaction occurs when the relationship between an environmental factor and a later health outcome depends on the individual's or parent's genotype.⁴⁶ Great interest in identifying the role of gene-environment interactions has been fueled by their potential to elucidate processes that underlie health outcomes.⁴⁷ Gene-environment interaction may provide insight into how environmental factors impact biological vulnerability for later outcomes, but the exact mechanisms underlying these effects are often unknown. Thus, the application of gene-environment interactions to medical and legal fields⁴⁸ is frequently limited by a lack of understanding of the biological mechanisms underlying these effects. Environmentally induced epigenetic modifications may represent the most promising biological mechanisms underlying gene-environment interactions.⁴⁹

II. EPIGENETICS OF MATERNAL SMOKING DURING PREGNANCY

A. EPIGENETIC MECHANISMS

“There are few situations during the life course where . . . gene-environment interactions[] are more striking than during prenatal development.”⁵⁰ There has been research to better understand the causes

44. Knopik, *supra* note 40, at 18.

45. *Id.*

46. Terrie E. Moffitt et al., *Strategy for Investigating Interactions Between Measured Genes and Measured Environments*, 62 *ARCHIVES GEN. PSYCHIATRY* 473, 473 (2005).

47. *Id.*

48. William Bernet et al., *Bad Nature, Bad Nurture, & Testimony Regarding MAOA & SLC6A4 Genotyping at Murder Trials*, 52 *J. FORENSIC SCI.* 1362, 1362 (2007).

49. See generally R.C. Bagot & M.J. Meaney, *Epigenetics & the Biological Basis of Gene × Environment Interactions*, 49 *J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY* 752 (2010).

50. Knopik et al., *supra* note 24, at 1377; see Matthew A. Maccani & Carmen J. Marsit, *Epigenetics in the Placenta*, 62 *AM. J. REPROD. IMMUNOLOGY* 78, 78 (2009) (“There are only a few settings where the importance of this gene-environment interface is more profound than during intrauterine development, where the ‘critical windows’ are narrower and where disruption or modification can influence fetal development as well as lead to programming of health throughout the life course.”).

and effects of DOHaD, including investigation into the molecular mechanisms of fetal programming with a special focus placed on epigenetics.⁵¹

Epigenetics is the study of changes in gene expression, or whether a gene is turned on or off, that are not caused by changes in the sequence of DNA.⁵² Recent research has suggested that epigenetic mechanisms may be the conduit through which environmental factors, like “stress, prenatal nutrition, or prenatal drug exposure can lead to changes in gene expression from one cell to its daughter cells and, in some cases, from one generation to the next.”⁵³ From such analyses, it has been hypothesized that epigenetics may be one mechanism through which fetal programming can occur.⁵⁴ Research has discovered four main modes of epigenetic gene regulation:⁵⁵ DNA methylation,⁵⁶ noncoding RNA-mediated gene regulation (especially by microRNA (“miRNA”)),⁵⁷ imprinting,⁵⁸ and histone modification.⁵⁹

51. See Maccani & Marsit, *supra* note 50, at 78.

52. Bird, *supra* note 3, at 396.

53. Knopik, *supra* note 40, at 1380. See generally Wadhwa, *supra* note 9, James M. Swanson et al., *Developmental Origins of Health & Disease: Environmental Exposures*, 27 SEMINARS IN REPROD. MED. 391 (2009).

54. See generally Bagot & Meaney, *supra* note 49.

55. For an extensive description of these epigenetic mechanisms, as well the technological advances that have made it possible to measure changes to these modes of epigenetic regulation which can result in changes to gene expression, see generally Maccani & Marsit, *supra* note 50.

56. DNA methylation is the most widely studied mode of epigenetic gene regulation. In brief, DNA methylation involves the attachment of methyl group (an organic compound) to cytosine (one of the four main bases of DNA) in cytosine/guanine-rich regions of DNA. A general rule—one that is usually, but not always, true—is that when cytosines in the promoter region of a gene are methylated, that gene will be effectively silenced by methylation (i.e., the gene would be turned “off”). Conversely, when a given stretch of cytosines in the promoter region of a gene are not methylated, that gene will not be silenced by methylation (i.e., the gene would remain turned “on”). Research suggests that it is not the methylation of DNA itself that contributes most to the shutting off of gene expression but rather the altered binding of various proteins to methylated stretches of DNA which leads to dysregulation of expression of genes. The removal and resetting of methylation patterns during embryonic development make the prenatal period an especially critical window during which the environment can have major effects on the offspring. See generally Maccani & Marsit, *supra* note 50; Matthew A. Maccani & Valerie S. Knopik, *Cigarette Smoke Exposure-Associated Alterations to Non-Coding RNA*, FRONTIERS GENETICS, Apr. 2012, at 1.

57. Ever since early discoveries of RNA as a product of the transcription of DNA, many have theorized that RNA may not only act as the intermediate step on the pathway from DNA to protein but may also have a degree of regulatory activity itself. Of the types of non coding RNA (“ncRNA”) involved in epigenetic gene regulation, the three best-characterized forms are microRNA (“miRNA”), Piwi-interacting RNA (“piRNA”), and long non-coding RNA (“long ncRNA”), with miRNA getting the most research attention to date. miRNA have been discovered in a variety of species and have been shown to be important regulators of a number of biological processes, including development, cell cycle regulation, and even cancer progression. miRNA function to regulate gene expression post-transcriptionally by base pairing to a target mRNA sequence. The specific mechanism of miRNA-mediated gene regulation appears to be dependent on a number of factors, the most important of which appears to be the degree of complementarity between the miRNA sequence and the target mRNA sequence. See generally Mariana Lagos-Quintana et al., *Identification of Novel Genes Coding*

for *Small Expressed RNAs*, 294 *SCIENCE* 853 (2001). As a general rule, perfect complementarity of a miRNA to its target mRNA sequence will result in the degradation of the mRNA transcript by a mechanism of Argonaute-catalyzed mRNA cleavage. See generally Gyorgy Hutvagner & Phillip D. Zamore, *A microRNA in a Multiple-Turnover RNAi Enzyme Complex*, 297 *SCIENCE* 2056 (2002); Ji-Joon Song et al., *Crystal Structure of Argonaute and Its Implications for RISC Slicer Activity*, 305 *SCIENCE* 1434 (2004); Soraya Yekta et al., *MicroRNA-Directed Cleavage of HOXB8 mRNA*, 304 *SCIENCE* 594 (2004). Imperfect sequence complementarity between a miRNA and its target mRNA will result in the translational repression of the target mRNA by blocking or altering the function of translational machinery through mechanisms, including the inhibition of translation initiation and poly(A) shortening. See generally Witold Filipowicz et al., *Mechanisms of Post-Transcriptional Regulation by microRNAs: Are the Answers in Sight?*, 9 *NATURE REV. GENETICS* 102 (2008); Lagos-Quintana et al., *supra* note 57. Due to the fact that partial or imperfect complementarity of a miRNA to a target mRNA can lead to translational repression which can effectively silence a gene, a single miRNA has been observed and speculated to have the capability of regulating a large number of genes. See Tingting Du & Phillip D. Zamore, *Beginning to Understand microRNA Function*, 17 *CELL RES.* 661 (2007). Some research has also pointed to the possibility that miRNA can utilize a combination of both translational repression and mRNA degradation as the mechanism for their post-transcriptional gene regulation, but more work is ongoing to more definitively characterize the mechanisms of miRNA-mediated regulation of gene expression. See generally Lee P. Lim et al., *Microarray Analysis Shows That Some microRNAs Downregulate Large Numbers of Target mRNAs*, 433 *NATURE* 769 (2005); Maccani & Marsit, *supra* note 50; Matthew A. Maccani & Carmen J. Marsit, *Exposure and Fetal Growth-Associated miRNA Alterations in the Human Placenta*, 2 *CLINICAL EPIGENETICS* 401 (2011); Maccani & Knopik, *supra* note 56.

58. Genomic imprinting is the parent-of-origin, allele-specific expression of genes. Imprinted genes are theorized to be controlled by both non-coding RNAs and changes in DNA methylation at sites in differentially methylated regions (“DMRs”). During imprinting, DNA methylation functions to alter the binding of specific transcription factor or enhancer elements (or both) that control the allele specific expression of the region. See generally Miguel Constanca et al., *Imprinting Mechanisms*, 8 *GENOME RES.* 881 (1998); Maccani & Marsit, *supra* note 50; Andrew J. Wood & Rebecca J. Oakey, *Genomic Imprinting in Mammals: Emerging Themes and Established Theories*, 2 *PLoS GENETICS* 1677 (2006). Imprinting has been hypothesized to be one of the mechanisms involved in the “parent conflict” theory. The “parent conflict theory” notes that paternally-expressed genes strongly promote the utilization of maternal resources to benefit offspring while maternally-expressed genes strongly promote the preservation of such maternal resources; thus, these parental influences are in direct conflict with one another. Using such logic, one might conclude that paternally-expressed (and maternally-imprinted) gene expression attempts to foster the growth of offspring while maternally-expressed (and paternally-imprinted) gene expression tries to ensure that each offspring has approximately the same access to maternal resources as its siblings. See generally C. Badcock & B. Crespi, *Imbalanced Genomic Imprinting in Brain Development: An Evolutionary Basis for the Aetiology of Autism*, 19 *J. EVOLUTIONARY BIOLOGY* 1007 (2006); Shirley M. Tilghman, *The Sins of the Fathers and Mothers: Genomic Imprinting in Mammalian Development*, 96 *CELL* 185 (1999). Genes regulated by imprinting are involved in a number of processes including embryonic and placental development and later-in-life functions such as behaviors and metabolism. Aberrant imprinting patterns have been described to lead to well-characterized syndromes (including Prader-Willi and Angelman Syndromes), altered establishment of imprinted genes (particularly at chromosome 11p15), and Beckwith-Wiedemann Syndrome, which has also been linked to the use of assisted reproductive technologies. See generally Aimee S. Chang et al., *Association Between Beckwith-Wiedemann Syndrome and Assisted Reproductive Technology: A Case Series of 19 Patients*, 83 *FERTILITY & STERILITY* 349 (2005); Michael R. DeBaun et al., *Association of In Vitro Fertilization with Beckwith-Wiedemann Syndrome and Epigenetic Alterations of LIT1 and H19*, 72 *AM. J. HUM. GENETICS* 156 (2003); Anthony R. Isles & Anthony J. Holland, *Imprinted Genes and Mother-Offspring Interactions*, 81 *EARLY HUM. DEV.* 73 (2005); E.R. Maher et al., *Beckwith-Wiedemann Syndrome and Assisted Reproduction Technology (ART)*, 40 *J. MED. GENETICS* 62 (2003); Benjamin Tycko & Ian M. Morison, *Physiological Functions of Imprinted Genes*, 192 *J. CELL PHYSIOLOGY* 245 (2002).

B. ENVIRONMENTAL EPIGENETICS

Epigenetic mechanisms have been investigated in a variety of settings. The subfield of “environmental epigenetics” studies how environmental exposures may affect epigenetic mechanisms.⁶⁰ A special focus of “environmental epigenetics” research has been to determine how environmental exposures during critical windows and sensitive periods of development, such as during pregnancy, might influence epigenetics and therefore affect the developing fetus and fetal programming.⁶¹ Research in both human cohorts and model systems (such as animals) continues to characterize the influence of environmental exposures on epigenetics. Prenatal exposures may, both directly and indirectly, influence fetal programming through epigenetic mechanisms. In addition, these epigenetic mechanisms, such as DNA methylation profiles or miRNA

59. Histone modifications involve the acetylation, methylation, phosphorylation, and ubiquitination of histone proteins around which DNA is wrapped, leading to regulation of gene expression. See generally Atsushi P. Kimura et al., *Epigenetic Modifications at the Human Growth Hormone Locus Predict Distinct Roles for Histone Acetylation and Methylation in Placental Gene Activation*, 18 *MOLECULAR ENDOCRINOLOGY* 1018 (2004); Bryan M. Turner, *Cellular Memory and the Histone Code*, 111 *CELL* 285 (2002). Such modifications of the amino-terminal tails of core histones by acetylation, phosphorylation, and methylation can determine gene activity by altering the accessibility of DNA to factors which can lead to (or repress) gene expression. See Thomas Jenuwein & C.D. Allis, *Translating the Histone Code*, 293 *SCIENCE* 1074 (2001); Brian D. Strahl & C.D. Allis, *The Language of Covalent Histone Modifications*, 403 *NATURE* 41 (2000); Yi Zhang & Danny Reinberg, *Transcription Regulation by Histone Methylation: Interplay Between Different Covalent Modifications of the Core Histone Tails*, 15 *GENES & DEV.* 2343 (2001). Histone methyltransferases—enzymes which aid in the transfer of methyl groups to histones—have been identified and characterized, including the H3-K4 methyltransferase and five H3-K9 methyltransferases. See generally Kenichi Nishioka et al., *Set9, a Novel Histone H3 Methyltransferase that Facilitates Transcription by Precluding Histone Tail Modifications Required for Heterochromatin Formation*, 16 *GENES & DEV.* 479 (2002); Hidesato Ogawa et al., *A Complex with Chromatin Modifiers that Occupies E2F- and Myc-Responsive Genes in G₀ Cells*, 296 *SCIENCE* 1132 (2002); Stephen Rea et al., *Regulation of Chromatin Structure by Site-Specific Histone H3 Methyltransferases*, 406 *NATURE* 593 (2000); David C. Schultz et al., *SETDB1: A Novel KAP-1-Associated Histone H3, Lysine 9-Specific Methyltransferase that Contributes to HP1-Mediated Silencing of Euchromatic Genes by KRAB Zinc-Finger Proteins*, 16 *GENES & DEV.* 919 (2002); Hengbin Wang et al., *Purification and Functional Characterization of a Histone H3-Lysine 4-Specific Methyltransferase*, 8 *MOLECULAR CELL* 1027 (2001); Liu Yang et al., *Molecular Cloning of ESET, a Novel Histone H3-Specific Methyltransferase that Interacts with ERG Transcription Factor*, 21 *ONCOGENE* 148 (2002). Researchers have also described a number of transcription co-activators that have characteristic histone acetyltransferase activity and histone deacetylases, which contribute to histone modification. See generally En Li, *Chromatin Modification and Epigenetic Reprogramming in Mammalian Development*, 3 *NATURE REV. GENETICS* 662 (2002). As a result, histone modifications can turn genes “on” or “off,” depending on which modification has been made. Alterations to patterns of histone modification can have a number of consequences, such as developmental dysregulation and diseases. Research is continuing to explore how normal and altered histone modifications can control gene expression, as well as how such modifications might be involved in regulating additional epigenetic processes and disease states. See generally Vincenzo Calvanese et al., *Cancer Genes Hypermethylated in Human Embryonic Stem Cells*, *PLoS ONE*, Sept. 2008, at 1.

60. Stella M. Reamon-Buettner et al., *The Next Innovation Cycle in Toxicogenomics: Environmental Epigenetics*, 659 *MUTATION RES.* 158, 159 (2008).

61. Knopik, *supra* note 24, at 1377–78.

expression, may have utility not only as diagnostic biomarkers capable of assessing levels of exposure to prenatal toxicants or predicting increased risk for behavioral deficits, diseases, or disease progression, but also as potential therapeutic targets.

C. HARMFUL PRENATAL EXPOSURES: MATERNAL SMOKING DURING PREGNANCY AND ASSOCIATED FETAL OUTCOMES

During prenatal development, the fetus is especially sensitive to harmful effects of a variety of exposures. The placenta, commissioned with the role of aiding the fetus during this critical time period, plays a crucial role in supporting the normal growth and development of the fetus. The placenta provides the fetus with nutrients, assists in waste removal, and exhibits a degree of metabolic activity that protects the fetus from both maternal immune rejection and from other environmental insults.⁶² As a center for metabolic activity, the placenta produces and secretes hormones that support each stage of pregnancy.⁶³ The placenta is also responsible for the reactions that ultimately protect the fetus from exposure to environmental toxicants.⁶⁴ A number of drugs and toxicants—including nicotine,⁶⁵ alcohol,⁶⁶ and benzo(a)pyrene⁶⁷—have been found to affect placental gene expression, thereby altering the ability of the placenta to ensure proper fetal growth and development.

Maternal cigarette smoking during pregnancy is associated with increased risk of a number of pregnancy complications such as spontaneous abortion,⁶⁸ preterm delivery,⁶⁹ and reduced birth weight.⁷⁰ Additional studies have shown that maternal cigarette smoking during pregnancy is associated with respiratory disease,⁷¹ asthma and allergies,⁷²

62. Matthew A. Maccani et al., *Maternal Cigarette Smoking During Pregnancy Is Associated with Downregulation of miR-16, miR-21, and miR-146a in the Placenta*, 5 EPIGENETICS 583, 583 (2010).

63. Maccani & Marsit, *supra* note 50, at 79.

64. *Id.*

65. Donna S. Lambers & Kenneth E. Clark, *The Maternal and Fetal Physiologic Effects of Nicotine*, 20 SEMINARS PERINATOLOGY 115, 119–21 (1996).

66. *See generally* John O. Beattie, *Transplacental Alcohol Intoxication*, 21 ALCOHOL & ALCOHOLISM 163 (1986).

67. *See generally* H.J. Guyda et al., *Benzo(a)pyrene Inhibits Epidermal Growth Factor Binding and Receptor Autophosphorylation in Human Placental Cell Cultures*, 37 MOLECULAR PHARMACOLOGY 137, (1990).

68. Anne Castles et al., *Effects of Smoking During Pregnancy: Five Meta-Analyses*, 16 AM. J. PREVENTIVE MED. 208, 211 (1999).

69. *Id.* at 212.

70. Matthew A. Maccani et al., *miR-16 and miR-21 Expression in the Placenta Is Associated with Fetal Growth*, PLOS ONE, June 2011, at 1, 5.

71. Derek G. Cook & David P. Strachan, *Summary of Effects of Parental Smoking on the Respiratory Health of Children and Implications for Research*, 54 THORAX 357, 357 (1999).

72. *See* Susan L. Prescott & Vicki Clifton, *Asthma and Pregnancy: Emerging Evidence of Epigenetic Interactions In Utero*, 9 CURRENT OPINION IN ALLERGY & CLINICAL IMMUNOLOGY 417, 417 (2009).

and cancer.⁷³ There are thousands of chemicals in cigarettes, including nicotine, benzo(a)pyrene and carbon monoxide; more than forty of these chemicals are known carcinogens.⁷⁴ Previous work has shown that nicotine can cross the placenta easily and can cause fetal concentrations that are fifteen percent higher than maternal concentrations.⁷⁵ Taken collectively, the vast body of literature describing the harmful effects of smoking during pregnancy suggests that maternal smoking remains a potentially dangerous common exposure that can have major ramifications not only on the normal growth and development of the fetus but also on fetal programming.⁷⁶

Although several studies have described a decrease in the overall prevalence of smoking in women in the past two decades, studies have also shown that the prevalence of smoking in young pregnant women under twenty years of age has increased to prevalence rates of thirty to forty percent.⁷⁷ Other studies have found that twelve to fifteen percent of all women of childbearing age smoke while pregnant.⁷⁸ In addition to the effects of primary smoke exposure (maternal smoking during pregnancy), it is necessary to consider the effects of secondhand smoke exposure on the developing fetus. Pregnant women and their fetuses may be exposed to secondhand smoke in homes, vehicles, the workplace, or public areas. Studies suggest that more than 126 million nonsmoking adults are exposed to secondhand smoke and that almost sixty percent of children ages three to eleven are exposed to secondhand smoke.⁷⁹ Collectively, cigarette smoke remains a common and hazardous exposure, especially at sensitive periods of development where exposure can have potentially serious, long-term effects on health.

In light of the plethora of scientific data suggesting negative consequences associated with smoking during pregnancy, pregnant women are cautioned against smoking while pregnant.⁸⁰ However, despite the

73. S. P. Doherty et al., *Early Life Insult From Cigarette Smoke May Be Predictive of Chronic Diseases Later in Life*, 14 *BIOMARKERS* 97, 99–100 (2009).

74. Anja Thielen et al., *Tobacco Smoke: Unraveling a Controversial Subject*, 60 *EXPERIMENTAL & TOXICOLOGIC PATHOLOGY* 141, 147 (2008).

75. Lambers & Clark, *supra* note 65, at 116.

76. Maccani, *supra* note 62, at 583.

77. Knopik, *supra* note 24, at 1378. See generally Niina Jaakkola et al., *Smoking During Pregnancy in Finland: Determinants and Trends, 1987–1997*, 91 *AM. J. PUB. HEALTH* 284 (2001); U.S. DEP'T HEALTH & HUMAN SERVS., *THE HEALTH CONSEQUENCES OF INVOLUNTARY EXPOSURE TO TOBACCO SMOKE: A REPORT OF THE SURGEON GENERAL* (2006).

78. Sven Cnattingius, *The Epidemiology of Smoking During Pregnancy: Smoking Prevalence, Maternal Characteristics, and Pregnancy Outcomes*, 6 *NICOTINE & TOBACCO RES.* 125, 127 (2004). See generally Renee D. Goodwin et al., *Mental Disorders and Nicotine Dependence Among Pregnant Women in the United States*, 109 *OBSTETRICS & GYNECOLOGY* 875 (2007).

79. Knopik, *supra* note 24, at 1378. See generally U.S. DEP'T HEALTH & HUMAN SERVS., *supra* note 77.

80. Knopik, *supra* note 24, at 1378. See generally Alison K. Shea & Meir Steiner, *Cigarette Smoking During Pregnancy*, 10 *NICOTINE & TOBACCO RES.* 267 (2008). See generally Marie D. Cornelius & Nancy L.

numerous research articles suggesting undesirable outcomes in children exposed to prenatal smoke exposure and warnings encouraging women to stop smoking while pregnant, a large percentage of women continue to smoke during pregnancy or are exposed to the dangers of secondhand smoke during pregnancy. Such figures, as well as the expenditure for smoking-associated health problems in mothers, fetuses, and children, beg for public health policy initiatives to more effectively communicate the potential dangers of smoking during pregnancy, as well as to better prevent the potentially harmful exposure to cigarette smoke altogether. Considerations for such public health campaigns, such as evidence-based policies for reducing maternal and paternal cigarette smoking during pregnancy through taxation of cigarettes, increasing public awareness, and smoking cessation interventions, are described later in this Article.

D. MATERNAL SMOKING DURING PREGNANCY: EPIGENETICS AS A POTENTIAL LINK TO FUTURE OUTCOMES?

A number of studies have investigated links between maternal smoking during pregnancy and aberrant epigenetic regulation of gene expression, with such dysregulation potentially associated with consequences for the fetus throughout the life course. Research by our group and others has characterized epigenetic alterations in target tissues associated with maternal cigarette smoking during pregnancy.

1. Maternal Smoking During Pregnancy and DNA Methylation

Studies of the human placenta have revealed associations between maternal cigarette smoking during pregnancy and DNA methylation in a gene specific and even global fashion. A group of researchers led by Melissa Suter from Baylor College of Medicine observed that maternal tobacco use is associated with aberrant placental epigenome-wide DNA methylation and gene expression.⁸¹ In a separate study, Suter and her colleagues described data suggesting that maternal tobacco smoking may modify placental cytochrome P450, family 1, subfamily A, polypeptide 1 (“CYP1A1”) expression by altering methylation at CpG sites proximal to the 50-xenobiotic response element transcription factor binding site.⁸² CYP1A1 is involved in the metabolism of carcinogenic compounds such as polycyclic aromatic hydrocarbons, which are present in cigarette smoke. This study found that the placentas of babies born to mothers

Day, *Developmental Consequences of Prenatal Tobacco Exposure*, 22 *CURRENT OPINIONS IN NEUROLOGY* 121 (2009).

81. See generally Melissa Suter et al., *Maternal Tobacco Use Modestly Alters Correlated Epigenome-Wide Placental DNA Methylation and Gene Expression*, 6 *EPIGENETICS* 1284 (2011).

82. See generally Melissa Suter et al. *In Utero Tobacco Exposure Epigenetically Modifies Placental CYP1A1 Expression*, 59 *METABOLISM* 1481 (2010).

who smoked during pregnancy had significantly lower methylation at these sites than babies born to nonsmoking mothers.⁸³ This relative decrease in methylation was also significantly correlated with increased placental CYP1A1 expression, a finding that may have substantial implications for future behavior.

Charlotte Wilhelm-Benartzi and colleagues showed that differential methylation of repetitive elements (stretches of DNA exhibiting a large number of repeated bases) in the placenta is associated with birth weight percentile and maternal smoking during pregnancy.⁸⁴ Specifically, they found that mean methylation levels of the repetitive element AluYb8 significantly differed by maternal tobacco use during pregnancy.⁸⁵ Overall, these reports suggest that cigarette smoke may elicit some of its downstream consequences on placental DNA methylation in both a global and site-specific fashion.

Associations between maternal smoking during pregnancy and DNA methylation have also been assessed using blood and specific cell types isolated from blood.⁸⁶ Y. Ba and colleagues used both maternal blood and umbilical cord blood to measure specific gene promoter methylation in insulin-like growth factor 2 (“IGF2”), which plays a growth factor role in the fetus.⁸⁷ These results suggested that IGF2 promoter methylation in the mother’s blood was associated with secondhand smoke exposure, as well as other covariates including vitamin B12 maternal blood serum levels and maternal weight gain during pregnancy.⁸⁸ Mary Beth Terry and colleagues investigated leukocyte (white blood cell) DNA methylation profiles in a multiethnic birth cohort from New York City.⁸⁹ Multivariable models suggested that overall levels of DNA methylation were significantly associated with maternal smoking during pregnancy and with other covariates.⁹⁰ Although such studies warrant replication in a larger cohort, thereby increasing their applicability and enhancing the ability to control for potential confounders, these studies of blood and blood-derived cells collectively provide preliminary data important for impelling future research into the utilization of DNA methylation

83. *Id.*

84. *See generally* Charlotte S. Wilhelm-Benartzi et al., *In Utero Exposures, Infant Growth, and DNA Methylation of Repetitive Elements and Developmentally Related Genes in Human Placenta*, 120 ENVTL. HEALTH PERSP. 296 (2012).

85. *Id.*

86. *See generally* Knopik, *supra* note 24.

87. *See generally* Y. Ba et al., *Relationship of Folate, Vitamin B12 and Methylation of Insulin-Like Growth Factor-II in Maternal and Cord Blood*, 65 EUR. J. CLINICAL NUTRITION 480 (2011).

88. *Id.*

89. *See generally* Mary Beth Terry et al., *Genomic DNA Methylation Among Women in a Multiethnic New York City Birth Cohort*, 17 CANCER EPIDEMIOLOGY, BIOMARKERS, & PREVENTION 2306 (2008).

90. *Id.*

patterns in cord blood or maternal blood as biomarkers of prenatal exposures like smoking.

Other researchers have also worked to characterize associations between maternal smoking during pregnancy and DNA methylation profiles linked to brain and neurodevelopmental outcomes. Maria Toledo-Rodriguez and colleagues investigated associations of maternal cigarette smoking during pregnancy and promoter methylation of brain-derived neurotrophic factor (“BDNF”) in blood samples from adolescents whose mothers had smoked during pregnancy.⁹¹ BDNF—which previous studies have shown is important for long-term memory—acts on certain neurons of the central nervous system and the peripheral nervous system, aids in supporting the survival of existing neurons, and encourages the growth and differentiation of new neurons and synapses.⁹² Toledo-Rodriguez and colleagues found that exposure to maternal cigarette smoking in utero is associated with a greater level of DNA methylation in the BDNF exon 6 in adolescents whose mothers smoked during pregnancy, suggesting that in utero cigarette smoke exposure may have long-term consequences still measurable into adolescence.⁹³ Such findings are especially intriguing in light of results suggesting that methylation of BDNF may have future utility as a diagnostic blood biomarker for depression.⁹⁴

Future work will continue to explore DNA methylation as a link between maternal cigarette smoking during pregnancy and future health outcomes. Such work will be necessary to further understand this link and to develop potentially powerful diagnostic biomarkers of both exposure and risk for future cigarette smoke exposure-associated disease.

2. *Maternal Smoking During Pregnancy and miRNA*

The body of literature characterizing associations between maternal cigarette smoking during pregnancy and miRNA is limited compared to the literature exploring associations with DNA methylation. Previous work by Maccani and colleagues used a candidate miRNA approach to measure changes in four human placental miRNA associated with maternal cigarette smoking during pregnancy, finding that maternal cigarette smoking during pregnancy was associated with decreased levels

91. Maria Toledo-Rodriguez et al., *Maternal Smoking During Pregnancy Is Associated with Epigenetic Modifications of the Brain-Derived Neurotrophic Factor-6 Exon in Adolescent Offspring*, 153B AM. J. MED. GENETICS PT. B 1350, 1350–54 (2010).

92. See generally Eric J. Huang & Louis F. Reichardt, *Neurotrophins: Roles in Neuronal Development and Function*, 24 ANN. REV. NEUROSCIENCE 677 (2001).

93. Toledo-Rodriguez et al., *supra* note 91, at 1352.

94. See generally Manabu Fuchikami et al., *DNA Methylation Profiles of the Brain-Derived Neurotrophic Factor (BDNF) Gene as a Potent Diagnostic Biomarker in Major Depression*, PLOS ONE, Aug. 2011, at 1.

of miR-16, miR-21, and miR-146a in the placenta.⁹⁵ They expanded their work to further explore which of the thousands of chemicals in cigarettes might be altering miRNA expression in placental cells, finding specifically that miR-146a was decreased in placental cells treated with nicotine and benzo(a)pyrene—two chemicals previously suggested to have negative consequences on the fetus.⁹⁶ As has been previously reviewed,⁹⁷ these observations were limited by sample size (here, 25), as well as lack of extensive data on daily cigarette smoke usage and exposure to other environmental toxicants.⁹⁸ Nonetheless, this analysis provides an important first investigation into associations between maternal cigarette smoking during pregnancy and altered placental miRNA expression. Future work investigating these associations in a larger sample set with more extensive exposure information will be key to further understand the impact of these associations and the consequences for the fetus throughout life.

3. Maternal Smoking During Pregnancy and Histone Modifications

Histone modifications have also been investigated for associations with maternal smoking during pregnancy. Virender Rehan and colleagues injected pregnant rats with nicotine and showed that the pups of these nicotine-exposed mothers developed asthma.⁹⁹ Similarly, when these pups were allowed to mature and breed, their resulting pups also developed asthma, suggesting that the effects of nicotine exposure may be transmitted across several generations even without direct exposure of an individual to nicotine.¹⁰⁰ The team found that one form of nicotine-induced acetylation of histone H3 could be blocked by a molecule known to protect lungs from asthma, suggesting that nicotine-induced acetylation of histone H3 might lead to asthma in both pups directly exposed to prenatal nicotine and future generations of pups as a result of the prenatal exposure of the pups' sex cells to nicotine.¹⁰¹ Future investigations will be key in order to further elucidate this relationship, especially to determine how exposure to cigarette smoke might continue to have negative consequences for future generations.

95. Maccani et al., *supra* note 62, at 583.

96. *Id.*

97. *See generally* Maccani & Marsit, *supra* note 57; Maccani & Knopik, *supra* note 56.

98. Maccani et al., *supra* note 62, at 583.

99. *See generally* Virender K. Rehan et al., *Perinatal Nicotine Exposure Induces Asthma in Second Generation Offspring*, 10 BMC MED. 129 (2012); *Grandma's Curse: Some of the Effects of Smoking May Be Passed From Grandmother to Grandchild*, THE ECONOMIST, Nov. 3, 2012, at 82.

100. *Id.*

101. *Id.*

E. EXPANDING PRENATAL CIGARETTE SMOKE-ALTERED EPIGENETICS TO POSTNATAL OUTCOMES

As previously noted, researchers have yet to fully explore epigenetic mechanisms which may underlie psychological disorders associated with maternal cigarette smoking during pregnancy.¹⁰² One model that might be further tested is that of “behavioral teratogenicity”—namely how fetal brain exposure to nicotine and the pathological activation of acetylcholine nicotinic receptors during early stages of brain development might lead to downstream neurobehavioral consequences.¹⁰³ Given that there is a high degree of comorbidity between nicotine dependence and neuropsychiatric conditions,¹⁰⁴ researchers have struggled to determine how influential exposure to cigarette smoke is on modulating risk for developing psychological disorders. Epigenetic mechanisms are one such pathway by which cigarette smoke could elicit harmful downstream effects on neurobehavior.

III. ETHICAL, POLICY, AND LEGAL CONSIDERATIONS

A. LEGAL EFFECTS OF PRENATAL CIGARETTE SMOKE EXPOSURE

Findings such as how the harmful effects of cigarette smoke exposure might be transmitted during prenatal development and across generations by epigenetic mechanisms introduce quite a number of ethical, policy, and legal questions. Prenatal exposure to cigarette smoke and grandmaternal transmission of the harmful effects of cigarette smoke (and many other toxicants) may lead to a larger discussion on negligence, criminal responsibility, and statutes of limitations.

To some readers, the notion of being held criminally responsible for using substances during pregnancy may seem hypothetical and speculative. However, at least thirty-four states’ legal statutes that were originally intended to protect children after birth from the dangers associated with methamphetamine labs and the trade and use of illicit drugs have been extended to protect the health of the fetus and prosecute mothers who use substances during pregnancy.¹⁰⁵ In a lengthy expose in the *New York Times* entitled “The Criminalization of Bad Mothers,” Ada Calhoun describes how states have applied child abuse statutes to effectively punish mothers who test positive for methamphetamines and other harmful substances

102. See generally Knopik, *supra* note 24.

103. See generally Rodrigo Paz et al., *Behavioral Teratogenicity Induced by Nonforced Maternal Nicotine Consumption*, 32 *NEUROPSYCHOPHARMACOLOGY* 693 (2007).

104. See generally Barbara Maughan et al., *Prenatal Smoking and Early Childhood Conduct Problems: Testing Genetic and Environmental Explanations of the Association*, 61 *ARCHIVES GEN. PSYCHIATRY* 836 (2004).

105. See generally Jean Reith Schroedel et al., *Women’s Rights and Fetal Personhood in Criminal Law*, 7 *DUKE J. GENDER L. & POL’Y* 89, 102 (2000).

while pregnant or during the delivery of their child.¹⁰⁶ Punishments range from fines to, in the most egregious cases or in the case of repeated offense, imprisonment.¹⁰⁷

Proponents of such practices argue that the punishments act as deterrents to such behavior, which has been shown in previous analyses to be associated with an increase in a child's postnatal complications and future neurobehavioral issues.¹⁰⁸ Supporters of these practices also argue that they have enacted such legislation to protect vulnerable members of society: children. Opponents of these practices cite studies that report that rates of mothers seeking prenatal care in states which have enacted such harsh legislation are decreasing.¹⁰⁹ Opponents argue that from a public health perspective, these findings suggest that such legal practices may do more harm than good for children in the long run. Furthermore, opponents stress that although substantial scientific evidence exists describing associations between prenatal drug exposures and postnatal outcomes, the vast majority of these findings are epidemiological in nature and such studies were not designed to test the causality of whether a drug exposure actually causes a downstream neurobehavioral outcome. Regardless of position on the issue, a level of caution, a consideration for legal precedent, the intent of the "bad actor," and a considerable knowledge of the body of scientific literature is necessary when considering legal practices that effectively criminalize negative maternal and paternal behavior during pregnancy.

Maternal substance use during pregnancy is also often viewed within the larger fetal rights debate, which includes the legal definition of personhood and laws related to abortion and fetal homicide.¹¹⁰ For example, given that a viable fetus is considered a "child" in the state of South Carolina, the Supreme Court of South Carolina ruled that maternal substance use during pregnancy could be prosecuted as child abuse.¹¹¹ In this domain, the maternal-fetal rights conflict stems from interventions aiming to improve fetal health trajectories by altering maternal behavior. Although these types of interventions aim to limit adverse prenatal environmental exposures (which may improve fetal health trajectories), opponents of such interventions argue that they also

106. Ada Calhoun, *The Criminalization of Bad Mothers*, N.Y. TIMES, Apr. 25, 2012, at MM30.

107. *Id.*

108. Cynthia Dailard & Elizabeth Nash, *State Responses to Substance Abuse Among Pregnant Women*, GUTTMACHER REP. PUB. POL'Y, Dec. 2000, at 1, 5.

109. See, e.g., Marilyn L. Poland et al., *Punishing Pregnant Drug Users: Enhancing the Flight From Care*, 31 DRUG & ALCOHOL DEPENDENCE 199, 202 (1993); U.S. GEN. ACCOUNTING OFFICE, GAO/HRD-90-198, DRUG-EXPOSED INFANTS: A GENERATION AT RISK, at 9-10 (1990).

110. See generally Schroedel, *supra* note 105.

111. *Whitner v. State*, 492 S.E.2d 777, 778 (S.C. 1997).

have the potential to infringe on women's autonomy and civil liberties.¹¹² The maternal-fetal rights conflict is often viewed as a zero sum game, meaning that any increase in fetal rights results in a decrease in maternal rights, and vice versa. In practice, however, interventions and policies may increase both maternal and fetal rights by increasing maternal autonomy and fetal health. Therefore, viewing maternal-fetal rights and health as complementary, rather than contrary, may allow for interventions and policies that are most effective in improving maternal-fetal health.¹¹³

In women, substance abuse disorder onset typically occurs prior to conception.¹¹⁴ Women who are substance dependent and become pregnant represent important candidates for substance use intervention, education, or possibly treatment.¹¹⁵ One's belief about what causes someone to use substances or smoke cigarettes may have an important impact on one's perceptions on the culpability and malleability of maternal smoking during pregnancy. Converging lines of evidence demonstrate that smoking initiation and nicotine dependence may be the result of both genetic *and* environmental influences;¹¹⁶ however, over one-third of individuals believe that genetics do not influence smoking behavior¹¹⁷ and hold overly simplified views of how substance abuse develops. Furthermore, other types of human behavior and traits are commonly viewed as having either genetic *or* environmental influences,¹¹⁸ a view which contradicts well-established behavioral genetic findings.

Oversimplified beliefs that contradict well-established scientific findings about what may influence deviant behavior, such as substance abuse, may have important legal implications. For example, if an individual is led to believe that deviant behavior has predominantly genetic origins they will be more likely to believe it is serious,¹¹⁹ determined, and immutable.¹²⁰ On the contrary, if deviant behavior is believed to result from non-genetic causes, the behavior is seen as more

112. Deborah Hornstra, *A Realistic Approach to Maternal-Fetal Conflict*, 28 HASTINGS CTR. REP. 7, 10 (1998).

113. Schroedel, *supra* note 105, at 117.

114. AM. SOC'Y ADDICTION MED., *Public Policy Statement on Women, Alcohol and Other Drugs, and Pregnancy*, 1 (July 11, 2011), http://www.asam.org/docs/public-policy-statements/1womenandpregnancy_7-11.pdf.

115. *Id.*

116. See generally Hermine H. Maes et al., *A Twin Study of Genetic and Environmental Influences on Tobacco Initiation, Regular Tobacco Use and Nicotine Dependence*, 34 PSYCHOL. MED. 1251 (2004).

117. Alison J. Wright et al., *Is Attributing Smoking to Genetic Causes Associated with a Reduced Probability of Quit Attempt Success? A Cohort Study*, 102 ADDICTION 1657, 1659 (2007).

118. Toby E. Jayaratne et al., *The Perennial Debate: Nature, Nurture, or Choice? Black and White Americans' Explanations for Individual Differences*, 13 REV. GEN. PSYCHOL. 24, 27 (2009).

119. Jo C. Phelan, *Geneticization of Deviant Behavior and Consequences for Stigma: The Case of Mental Illness*, 46 J. HEALTH & SOC. BEHAV. 307, 317 (2005).

120. Ilan Dar-Nimrod & Steven J. Heine, *Genetic Essentialism: On the Deceptive Determinism of DNA*, 137 PSYCHOL. BULL. 800, 802 (2011).

voluntary, blameworthy, and is elected to receive more severe punishments.¹²¹ Together, these findings suggest that people's causal attributions of deviant behavior often lack an empirical basis and alter beliefs about personal responsibility and appropriate punishment. These biases highlight the importance of understanding that the majority of health and behavior outcomes are the result of genetic *and* environmental factors, which are both statistically and functionally related. For example, genetic factors may predispose individuals to be exposed to particular environments¹²² and environmental exposures influence biological vulnerability through a number of mechanisms.

In moving forward with translating scientific findings into effective public health policy, a special focus should be given to prevent harmful prenatal exposures, where possible, in the first place, thereby promoting fetal health and protecting future children; at the same time, maternal and paternal rights need to be acknowledged and protected.

B. INTERVENTIONS TO REDUCE CIGARETTE SMOKE EXPOSURE IN EARLY DEVELOPMENT

A variety of interventions are aimed at increasing rates of smoking cessation and reducing rates of smoking initiation. The Centers for Disease Control and Prevention ("CDC") recommends a multi-pronged approach, including state and community-level interventions, health communication, and cessation programs, as well as mechanisms to both manage and evaluate such interventions.¹²³ The following discussion is not meant to endorse a specific approach to intervention, but rather to highlight the relative costs and benefits of approaches that reduce rates of smoking in both the general population and in pregnant women.

1. Legislative Interventions

Tobacco control spending,¹²⁴ tobacco counter-marketing, cigarette excise taxes, and restricting smoking in public places all represent cost-effective policies that influence smoke exposure in the population.¹²⁵ The CDC program suggestions¹²⁶ indicated that higher level and longer periods of tobacco control spending were related to a greater reduction in smoking prevalence. Every dollar spent on tobacco control spending

121. Phelan, *supra* note 119, at 316–17.

122. Kendler & Baker, *supra* note 41, at 620–21.

123. CTRS. FOR DISEASE CONTROL & PREVENTION, BEST PRACTICES FOR COMPREHENSIVE TOBACCO CONTROL PROGRAMS 7, 34 (2007).

124. Tobacco control spending refers to state and federal money that is used to support efforts to prevent or reduce tobacco use.

125. Jennifer W. Kahende et al., *A Review of Economic Evaluations of Tobacco Control Programs*, 6 INT'L J. ENVTL. RES. & PUB. HEALTH 51, 54–63 (2009).

126. CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 123, at 9.

has been estimated to be associated with a health care savings of approximately five dollars.¹²⁷ To the extent that fetal and child exposure to smoking puts individuals at risk for later negative health and behavioral outcomes, and that risk may be transmitted between generations, current cost-effectiveness measures may underestimate the benefits of such programs.

Adams and colleagues found that level of tobacco control spending was associated with lower postpartum smoking in older mothers; however, there was no relationship between tobacco control spending level and reported prenatal smoking.¹²⁸ One explanation for this is that state spending does not reach CDC recommendations,¹²⁹ while another possibility may be that states are failing to most effectively channel funds currently designated for tobacco control—for example, by investing in programs that consistently underperform or are not effective in improving tobacco control. The CDC estimates that states need to spend between \$9.23 and \$18.02 per capita to implement an effective comprehensive tobacco control program.¹³⁰ Currently, the majority of states are spending far below such estimates.¹³¹ Despite record levels of tobacco revenue from taxes and the 1998 Tobacco Master Settlement Agreement,¹³² current tobacco control spending has decreased over the past decade. Currently, less than two percent of tobacco related revenue is spent on prevention and tobacco cessation programs,¹³³ which is associated with state revenues.¹³⁴ However, in addition to state revenue, state tobacco control spending is associated with the level of state tobacco production and campaign contributions from tobacco lobbies.¹³⁵ These findings suggest that tobacco special interest groups may make it more difficult for states to reach spending levels that are needed to

127. Julia A. Dilley et al., *Program, Policy, and Price Interventions for Tobacco Control: Quantifying the Return on Investment of a State Tobacco Control Program*, 102 AM. J. PUB. HEALTH 22, 24 (2012).

128. E. Kathleen Adams et al., *Reducing Prenatal Smoking: The Role of State Policies*, 43 AM. J. PREVENTIVE MED. 34, 39 (2012).

129. *Id.*

130. CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 123, at 15. According to the CDC, best practices to reduce tobacco use were created from an “evidence-based analyses of scientific literature and outcomes of comprehensive state tobacco control programs and interventions.” *Id.* at 14. For an overview on how recommended funding levels for each state were determined, see *id.* at 111–12.

131. CAMPAIGN FOR TOBACCO-FREE KIDS, *BROKEN PROMISES TO OUR CHILDREN: THE 1998 STATE TOBACCO SETTLEMENT 14 YEARS LATER* i (2012).

132. *See, e.g.*, CAL. HEALTH & SAFETY CODE §§ 104555–58 (2000) (codifying California’s adoption of the Master Settlement Agreement).

133. Sabrina Tavernise, *States Cut Antismoking Outlays Despite Record Tobacco Revenue*, N.Y. TIMES, Dec. 6, 2012, at A.19.

134. Adam J. Hoffer & Adam Pellillo, *The Political Economy of Tobacco Control Spending*, 19 APPLIED ECON. LETTERS 1793, 1795 (2012).

135. *Id.* at 1796.

implement the effective tobacco control programs described by the CDC.¹³⁶

Tobacco counter-marketing and marketing restrictions also aim to reduce smoking initiation and increase smoking cessation. In the United States, current tobacco health warning labels have remained largely unchanged since 1984 and are easily overlooked.¹³⁷ Four different cigarette health warnings in text are currently placed on the side of United States cigarette packs. In contrast, more prominent pictorial and text cigarette health warnings labels have been utilized in at least forty-five countries. Investigative analyses suggest that these health warning labels effectively increase thoughts about quitting and may decrease smoking rates.¹³⁸ In addition, pictorial cigarette health warnings have been shown to increase intentions to quit across a variety of socio-demographic and racial or ethnic groups.¹³⁹ In 2009, The Family Smoking Prevention and Tobacco Control Act introduced additional marketing restrictions on tobacco products and granted the Food and Drug Administration (“FDA”) the authority to regulate tobacco-related marketing.¹⁴⁰ As a result, the FDA mandated that nine new pictorial and text labels be included on cigarette packages beginning September 2012.¹⁴¹ For example, one label reads “WARNING: SMOKING DURING PREGNANCY CAN HARM YOUR BABY” and is accompanied by a cartoon picture of a baby in an incubator.¹⁴² The D.C. district court, however, found that the FDA mandate violated the tobacco company’s First Amendment rights.¹⁴³ This decision was upheld by a divided court of appeals which cited insufficient evidence that pictorial cigarette warning labels reduced smoking rates.¹⁴⁴ The future use of more graphic tobacco health warnings in this country remains unclear and additional research into the influence of graphic tobacco health warnings on rates of smoking initiation and cessation is needed.

136. See generally CENTERS FOR DISEASE CONTROL & PREVENTION, *supra* note 123.

137. Jennifer Cantrell et al., *Impact of Tobacco-Related Health Warning Labels Across Socioeconomic, Race and Ethnic Groups: Results from a Randomized Web-Based Experiment*, PLoS ONE, Jan. 2013, at 1, 1; Thomas N. Robinson & Joel D. Killen, *Do Cigarette Warning Labels Reduce Smoking? Paradoxical Effects Among Adolescents*, 151 ARCHIVES PEDIATRICS & ADOLESCENT MED. 267, 271–72 (1997).

138. David Hammond, *Health Warning Messages on Tobacco Products: A Review*, 20 TOBACCO CONTROL 327, 332 (2011); David Hammond et al., *Communicating Risk to Smokers: The Impact of Health Warnings on Cigarette Packages*, 32 AM. J. PREVENTIVE MED. 1, 5–6 (2007).

139. See generally Cantrell, *supra* note 137.

140. Pub. L. No. 111-31, 123 Stat. 1776, 1777 (2009) (codified as amended at 21 U.S.C. §§ 387–87u (2009)).

141. *Id.* § 201(d).

142. *Cigarette Health Warnings*, FOOD & DRUG ADMIN., <http://www.fda.gov/downloads/TobaccoProducts/Labeling/UCM259401.pdf> (last visited July 30, 2013).

143. R.J. Reynolds Tobacco Co. v. FDA, 845 F. Supp. 2d 266, 277 (D.D.C. 2012).

144. R.J. Reynolds Tobacco Co. v. FDA, 696 F.3d 1205, 1222 (D.C. Cir. 2012).

Research has shown that increases in cigarette excise taxes may reduce the prevalence of smoking in the general population.¹⁴⁵ In addition, one group of researchers found that amongst pregnant women, a one dollar increase in cigarette taxes was associated with a 4.8% increase in the probability of smoking cessation by the third trimester, an effect that remained largely intact four months after delivery.¹⁴⁶ Furthermore, the relationship between increased cigarette taxes and increased smoking cessation did not depend on maternal education, level of pre-pregnancy smoking, or parity.¹⁴⁷ Parallels have been observed in the context of raising minimum prices of alcohol, which could offer hope for the potential effectiveness of such increased pricing on reducing harms associated with dangerous substances of abuse. In British Columbia, a 10% increase in the minimum price for the least expensive alcoholic beverages led to a 3.4% decrease in consumption of alcoholic beverages¹⁴⁸ and a 31.7% decrease in alcohol attributable deaths.¹⁴⁹ Together, these findings suggest that increasing cigarette excise taxes may help to reduce smoking rates and smoking-related morbidity and mortality.

Smoking bans in public places (such as restaurants and bars) represent another legislative intervention which may impact maternal smoking during pregnancy in public places. In addition to the social stigma associated with smoking in public during pregnancy,¹⁵⁰ this type of legislation may be another barrier to smoking in public during pregnancy. Evidence suggests that smoking bans in public places are generally associated with increased smoking cessation, as well as decreased tobacco consumption and secondhand smoke exposure.¹⁵¹ In addition, full smoking bans in private workplaces were associated with a 5% increase in the probability that an expecting mother would quit smoking by the third trimester.¹⁵² Taken together, smoking bans in public places may offer another effective means for reducing fetal exposure to

145. See generally F.J. Chaloupka et al., *Effectiveness of Tax and Price Policies in Tobacco Control*, 20 *TOBACCO CONTROL* (2011).

146. Adams et al., *supra* note 128, at 37.

147. See generally T. Coleman et al., *Pharmacological Interventions for Promoting Smoking Cessation During Pregnancy*, 9 *COCHRANE DATABASE SYSTEMATIC REV.* (2012).

148. Tim Stockwell et al., *Does Minimum Pricing Reduce Alcohol Consumption? The Experience of a Canadian Province*, 107 *ADDICTION* 912, 916 (2012).

149. See generally Jinhui Zhao et al., *The Relationship Between Minimum Alcohol Prices, Outlet Densities and Alcohol Attributable Deaths in British Columbia, 2002–09*, 108 *ADDICTION* 1059 (2013).

150. Leona Bull, et al., *Social Attitudes Towards Smoking in Pregnancy in East Surrey: A Qualitative Study of Smokers, Former Smokers and Non-Smokers*, 13 *J. NEONATAL NURSING* 100, 101 (2007).

151. See generally Joanne E. Callinan et al., *Legislative Smoking Bans for Reducing Secondhand Smoke Exposure, Smoking Prevalence and Tobacco Consumption (Review)*, *COCHRANE DATABASE SYSTEMATIC REV.* (2010).

152. Adams et al., *supra* note 127, at 34–35.

smoke in utero by reducing maternal rates of smoking and by reducing the level of secondhand smoke exposure.

2. *Smoking Cessation Treatment*

Smoking cessation programs have also been shown to increase rates of smoking cessation among smokers looking to quit.¹⁵³ Proactive interventions for smokers who are not ready to quit, however, are less likely to be effective.¹⁵⁴ Smoking cessation programs for pregnant women also increase smoking cessation; however, across the most well-controlled studies (randomized clinical trials and biochemical validation of smoking cessation), the mean smoking cessation rate is only four percent.¹⁵⁵ Although smoking cessation treatments are more effective in increasing rates of smoking cessation compared to placebos, there is still a need to enhance the effectiveness of such programs.

Smoking cessation programs may also include pharmacotherapy. For example, nicotine replacement therapy (including patches or gum) may be effective in increasing smoking cessation in the general population, as both a supplement and an independent treatment.¹⁵⁶ The safety of nicotine replacement therapy in pregnant mothers, however, is currently controversial.¹⁵⁷ An initial report linked first trimester use of nicotine replacement therapy with increased congenital malformations,¹⁵⁸ but a recent meta-analysis found that the relationship between nicotine replacement therapy and perinatal outcomes is currently inconclusive.¹⁵⁹ Although other pharmacotherapies for smoking cessation exist (such as bupropion and varenicline), the effectiveness and side effects of these drugs have not been rigorously examined in pregnant mothers.

In order to further reduce smoking during pregnancy, it is also important to consider that many psychosocial risk factors are associated with maternal smoking during pregnancy including¹⁶⁰ less education,¹⁶¹

153. Jerry M. Suls et al., *Efficacy of Smoking-Cessation Interventions for Young Adults: A Meta-Analysis*, 42 AM. J. PREVENTATIVE MED. 655, 660–61 (2012).

154. Lisa Sanderson Cox et al., *Predictors of Early Versus Late Smoking Abstinence Within a 24-Month Disease Management Program*, 13 NICOTINE & TOBACCO RES. 215, 218 (2011).

155. KB Filion et al., *The Effect of Smoking Cessation Counselling in Pregnant Women: a Meta-analysis of Randomised Controlled Trials*, 118 BJOG: INT'L J. OBSTETRICS & GYNAECOLOGY 1422, 1424 (2011).

156. See generally L.F. STEAD & T. LANCASTER, *Combined Pharmacotherapy and Behavioural Interventions for Smoking Cessation*, THE COCHRANE LIBR. (2012).

157. See generally Coleman et al., *supra* note 147.

158. See generally Maria M. Morales-Suárez-Varela et al., *Smoking Habits, Nicotine Use, and Congenital Malformations*, 107 OBSTETRICS & GYNECOLOGY 51 (2006).

159. See generally Coleman et al., *supra* note 147.

160. Valerie S. Knopik, *Commentary: Smoking During Pregnancy—Genes and Environment Weigh In*, 39 INT'L J. EPIDEMIOLOGY 1203, 1203–04 (2010).

161. Brian M. D'Onofrio et al., *A Quasi-Experimental Study of Maternal Smoking During Pregnancy and Offspring Academic Achievement*, 81 CHILD DEV. 80, 89 tbl.2 (2010).

substance dependence and psychiatric comorbidity,¹⁶² having a substance dependent partner,¹⁶³ and having a history of criminal conviction.¹⁶⁴ This suggests that maternal smoking during pregnancy may be maintained, in part, by other psychosocial factors and that maternal smoking during pregnancy may be a way that mothers cope with such stressors.¹⁶⁵ Mothers who continue to smoke during pregnancy tend to smoke more and experience more psychosocial stress than mothers who quit smoking during pregnancy.¹⁶⁶ Thus, to increase the effectiveness of interventions aimed at reducing maternal smoking during pregnancy, it is important to also target psychosocial stressors that may contribute to mothers maintaining their smoking during pregnancy.

CONCLUSION

The growing application of the DOHaD hypothesis¹⁶⁷ and inclusion of epigenetic profiling in health and behavioral studies has great potential for improving public health. Specifically, the DOHaD paradigm emphasizes the importance of early environmental influences, especially prenatal and intergenerational environmental effects, in influencing vulnerability for later health outcomes. Additionally, epigenetic mechanisms provide insight into how the environment may “get under the skin” to influence gene expression and vulnerability for later health outcomes. DOHaD and epigenetic research findings may have wide-ranging applications in legal policy and practice. Such findings may easily be misunderstood or misinterpreted, however, due to the complex relationships among maternal smoking during pregnancy, epigenetic regulation, and later health outcomes. Therefore, any application of these findings to legal policy and practice requires great care, as well as a thorough understanding of multiple scientific disciplines and legal precedents.

This Article provides an overview of scientific findings examining the interrelationships between maternal smoking during pregnancy, epigenetic regulation, and health related outcomes. Maternal smoking

162. Arpana Agrawal et al., *Correlates of Cigarette Smoking During Pregnancy and its Genetic and Environmental Overlap with Nicotine Dependence*, 10 NICOTINE & TOBACCO RES. 567, 573–76 (2008).

163. Valerie S. Knopik et al., *Contributions of Parental Alcoholism, Prenatal Substance Exposure, and Genetic Transmission to Child ADHD Risk: A Female Twin Study*, 35 PSYCHOL. MED. 625, 630 (2005).

164. Brian M. D’Onofrio et al., *Familial Confounding of the Association Between Maternal Smoking During Pregnancy and Offspring Criminality: A Population-Based Study in Sweden*, 67 ARCHIVES GEN. PSYCHIATRY 529, 532–33 (2010).

165. William D. Lopez et al., *Abuse-Related Post-Traumatic Stress, Coping, and Tobacco Use in Pregnancy*, 40 J. OBSTETRIC, GYNECOLOGIC & NEONATAL NURSING 422, 425 (2011).

166. See generally Kate E. Pickett et al., *The Psychosocial Context of Pregnancy Smoking and Quitting in the Millennium Cohort Study*, 63 J. EPIDEMIOLOGY & COMMUNITY HEALTH 474 (2009).

167. Peter Gluckman & Mark A. Hanson, *Living with the Past: Evolution, Development, and Patterns of Disease*, 305 SCIENCE 1733, 1733 (2004).

during pregnancy and other forms of pre- and postnatal smoke exposure continue to be associated with negative health consequences.¹⁶⁸

Findings linking maternal smoking during pregnancy with aberrant patterns of epigenetic regulation provide insight into how prenatal smoke exposure may alter vulnerability for later health outcomes.¹⁶⁹ Furthermore, negative health sequelae associated with cigarette smoke exposure may be transmitted from one generation to the next,¹⁷⁰ potentially through intergenerational epigenetic effects.¹⁷¹ These findings may provide insight into the nature of the relationship between maternal smoking during pregnancy and subsequent offspring health outcomes. Due to the study design limitations of several of the human studies discussed, it should be noted that these studies were unable to test for a *causal* relationship between maternal smoking during pregnancy and later health outcomes; therefore, special care should be taken in interpreting the results of such epidemiological studies. Additional experimental studies investigating the interrelationships between maternal smoking during pregnancy, epigenetic regulation, and offspring health outcomes may be needed to test for a causal relationship between maternal smoking during pregnancy and later health outcomes.

Bearing these limitations in mind, findings linking maternal smoking during pregnancy to aberrant epigenetic regulation or later offspring health outcomes pose important ethical, legal, and policy questions. A conflict in maternal-fetal rights may arise when maternal substance use leads to a decline in the fetus's health trajectory or when attempts to promote fetal health trajectories infringe on an expecting mother's autonomy.¹⁷² To promote fetal health, a variety of states have criminally prosecuted mothers who abused substances during pregnancy.¹⁷³ However, this practice may have paradoxical effects on fetal health because mothers who use substances during pregnancy may be less likely to seek prenatal care if they may suffer the consequences of prosecution as a result of the criminalization of maternal substance use during pregnancy.¹⁷⁴ Although maternal and fetal rights are often viewed in opposition to one another—as in the case of abortion—this does not necessarily hold true for maternal substance use during pregnancy.¹⁷⁵ Viewing maternal-fetal rights and health as complementary may allow

168. See generally Knopik, *supra* note 24.

169. *Id.* at 1379–81.

170. Misra et al., *supra* note 8, at 291–92.

171. Rehan et al., *supra* note 99, at 139.

172. See generally Hornstra, *supra* note 112.

173. Calhoun, *supra* note 106.

174. Poland et al., *supra* note 109, at 201–02.

175. See generally Schroedel et al., *supra* note 105.

for more effective legal policies and interventions aimed at improving fetal health trajectories.

There are a variety of effective interventions aimed at reducing levels of maternal smoking during pregnancy that do not infringe on maternal autonomy. The CDC recommends a multi-level approach for reducing the public health impact of smoking.¹⁷⁶ Tobacco control spending, tobacco excise taxes, and smoking bans are all associated with decreased smoking in expecting mothers and mothers who recently gave birth.¹⁷⁷ Specifically, increasing the price of cigarettes by one dollar led to a four to five percent increase in smoking cessation among expecting mothers.¹⁷⁸ These initiatives have been shown to be effective in increasing smoking cessation in a small but meaningful percentage of women who smoke during pregnancy. Smoking cessation programs targeted specifically at women of child bearing age or those who are expecting may further reduce rates of prenatal smoke exposures.

Smoking cessation therapy is effective in the general population of smokers who are motivated to quit¹⁷⁹ and leads to an approximately 4% increase in smoking cessation rates among pregnant women.¹⁸⁰ Smoking cessation programs targeting smokers who are not ready to quit are less likely to be effective.¹⁸¹ Given that maternal substance use during pregnancy is associated with a host of additional psychosocial stressors,¹⁸² interventions aimed at reducing smoking during pregnancy may require a more comprehensive approach, which addresses factors that serve to maintain maternal substance use during pregnancy and beyond.

In summary, there is a substantial body of evidence linking maternal smoking during pregnancy with a variety of negative offspring health outcomes. Epigenetic mechanisms may: (1) help to explain how prenatal smoke exposure influences biological vulnerability for later health outcomes, and (2) be involved in the transmission of the negative effects of prenatal smoke exposure from one generation to the next. Legal policy and practice will continue to shape the impact that current and future epigenetic findings linking prenatal exposures to harmful postnatal outcomes will have on both fetal and maternal health. Scientifically-informed policy and legal practice will be important as policy makers strive to reduce the harms associated with prenatal smoke exposure and strike the appropriate balance in the maternal and fetal rights debate.

176. CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 123, at 7, 34.

177. Adams et al., *supra* 128, at 37.

178. *Id.*

179. Suls et al., *supra* note 153, at 661.

180. Filion et al., *supra* note 155, at 1424.

181. Cox et al., *supra* note 154, at 218.

182. Knopik *supra* note 160, at 1203–04.