Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years: Workshop in Brief

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Examining a Developmental Approach to Childhood Obesity: The Fetal and Early Childhood Years—Workshop in Brief

Recent scientific evidence points to the origins of childhood obesity as an outcome of the dynamic interplay of genetic, behavioral, and environmental factors, with a compelling body of evidence suggesting that both maternal and paternal nutritional and other exposures affect a child's risk of obesity. The burgeoning field of epigenetics has led researchers to speculate that many known associations between early developmental exposures and later risk of childhood obesity are mediated, at least in part, through epigenetic mechanisms.[1] On February 26–27, 2015, the Institute of Medicine (IOM) Food and Nutrition Board and the IOM and the National Research Council Board on Children, Youth, and Families convened a workshop in Washington, DC, to explore the body of evolving science that examines the nexus of biology, interaction between biology and environment, and developmental stage on risk for childhood obesity. The workshop focused on the prenatal period, infancy, and early childhood and evidence from animal and human studies. The workshop objectives developed by the planning committee were to (1) identify epigenetic-mediated relationships between exposure to risk factors during sensitive periods of development (gestation through age 3) and subsequent obesity-related health outcomes; (2) explore the science around periods of plasticity and potential reversibility of obesity risk in the context of early childhood development; and (3) examine the translation of epigenetic science to guide early childhood obesity prevention and intervention to reduce obesity risk. This workshop in brief highlights key points made during the workshop presentations and discussion.[2] The information and suggestions for future action summarized here reflect the knowledge and opinions of individual workshop participants and should not be construed as consensus.

Opening Remarks

In her welcome remarks, Shari Barkin, Monroe Carell Jr. Children's Hospital at Vanderbilt University, emphasized the dynamic nature of the multiple external and internal factors that interact to cause childhood obesity and encouraged workshop participants to consider how scientists' growing knowledge of these dynamic interactions, with differing degrees of influence depending on the stage of child development, can shed light on where to target childhood obesity prevention efforts during periods of plasticity and potential reversibility (see Figure 1). Currently, pediatricians rely on what Sandra Hassink, American Academy of Pediatrics, in her opening remarks referred to as "very blunt instruments" for preventing childhood obesity, namely food and exercise. Hassink stated that clinicians need better intervention tools to meet current needs, especially given the very complex socio-ecological milieu of childhood obesity. Part of that complexity, as both Hassink and Jamie Bussel, Robert Wood Johnson Foundation, emphasized, stems from the challenges created by the massive disparities in obesity prevalence. Bussel stated that although there has been recent progress in reducing childhood obesity rates, it has been shared unequally, with

[1] Shari Barkin defined epigenetics as "changes in gene expression via changes in post-translational and post-transcriptional modifications." Robert Waterland defined epigenetics as "the study of mitotically heritable stable alterations in gene expression potential that are not caused by changes in DNA sequence." However, many workshop participants used "epigenetics" in its broadest sense, that is, in reference to biological phenomena that can be attributed to more than just what genes are present but also whether and how those genes actually are expressed. Derived from the Greek prefix "epi-," epigenetics literally means "above genetics."

[2] A comprehensive summary of the workshop will be publicly available in a forthcoming publication.

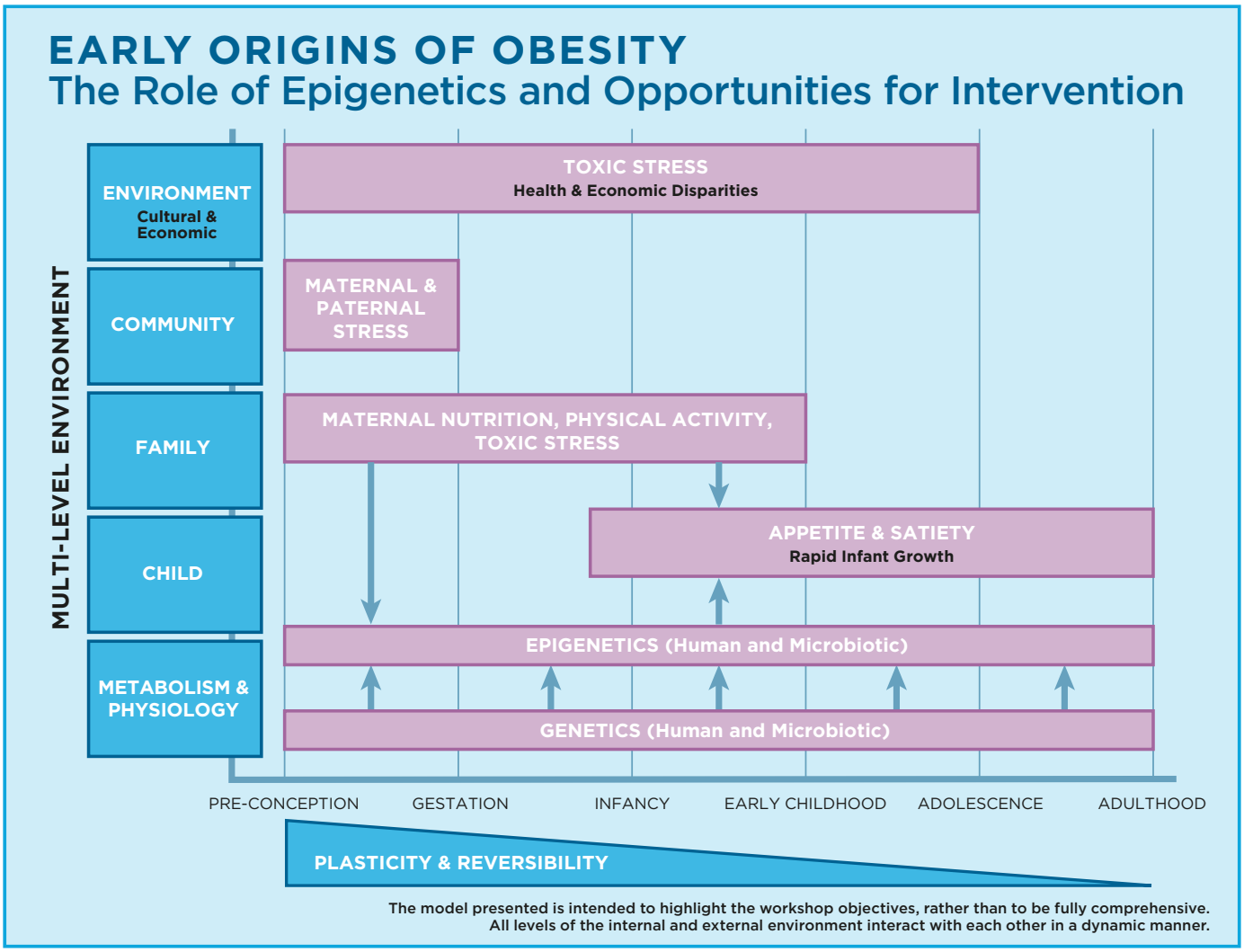

FIGURE 1 Early origins of obesity: Multiple external and internal factors interact to cause childhood obesity.

white children and children in high-income areas showing greater decreases in risk of obesity. She emphasized the importance of intervening early, including working with parents before babies are born, and expressed hope that the workshop would help to build a stronger understanding of the relationship between early development and obesity.

Although epigenetics is considered by many to be an emerging field of research, in his opening remarks David Klurfeld, U.S. Department of Agriculture, reminded workshop participants of the long history of studying genes in their broader context and referred workshop participants to the "forgotten father" of epigenetics, Ernest Just, an embryologist of the early 20th century.

Conceptual Overview of the Role of Epigenetics in Pediatric Obesity

Much of the workshop discussion revolved around the emerging nature of the evidence for epigenetics as a key component of the "early origins of obesity" model (featured in Figure 1, the workshop infographic) and whether experimental findings indicate causal versus correlational or confounding associations. Session 1, moderated by Matthew Gillman, Harvard School of Public Health, set the conceptual stage for this discussion.

Robert Waterland, Baylor College of Medicine, described arguably the clearest example of the causal role of epigenetic dysregulation in obesity in an animal model: genetically identical agouti mice developing into either lean

(and brown) or obese (yellow) mice depending on the degree of DNA methylation[3] at the agouti locus. Waterland cautioned, however, that there are a multitude of obstacles to understanding how epigenetic dysregulation might similarly cause obesity in humans. For researchers conducting human studies, he encouraged performing prospective studies to help infer causality, assessing epigenetic variation within the context of genetic variation, and focusing on tissue-specific epigenetic patterning.

Andrea Baccarelli, Harvard School of Public Health, elaborated on the challenge of differentiating causality from correlation. He described a recent study where the authors associated methylation of a gene in fat tissue with body mass index (BMI) but concluded that methylation did not determine BMI, rather BMI determined methylation, a reverse causality. Baccarelli expressed hope that in the future, epigenetic markers at birth can be used to identify newborns at increased risk of childhood obesity. But again, as Waterland had cautioned, many obstacles will need to be overcome before reaching that clinical point. Baccarelli speculated that epigenetics might be experiencing the same "winner's curse" that the field of genetics experienced when geneticists started reporting genome-wide associations between genomic patterning and disease; initially, many reported effect sizes were overestimated with a smaller effect size made evident through repeated large-scale studies.

Etiology and Causal Inference

Following Waterland's and Baccarelli's conceptual overview, workshop participants in Session 2, moderated by Karen Lillycrop, University of Southampton, considered how the risk of childhood obesity can be affected by (1) maternal and paternal nutrition and other exposures before conception, (2) maternal and placental nutrition and health during pregnancy, and (3) postnatal maternal and infant nutrition and health.

"Obesity begets obesity," began Jacob Friedman, University of Colorado, Denver. Friedman discussed animal and human data demonstrating that both prenatal and postnatal exposure to maternal obesity predispose infants to early onset metabolic disease and childhood obesity. For example, studies conducted on obese pregnant mothers indicate that pre-pregnancy BMI of the mothers, not infant BMI, is predictive of higher infant liver fat at 2 months of age. Friedman explained that maternal fuels crossing the placenta have nowhere to go but into the fetal liver and suggested that this fatty liver trans-generational effect of maternal obesity may be mediated by epigenetic changes in offspring liver cells. Postnatally, evidence from breastfeeding mothers indicates that maternal obesity has an effect on the infant microbiome in a way that may, via epigenetic mechanisms, increase infant adiposity.

Linda Adair, School of Public Health at the University of North Carolina, described inequities among different socioeconomic groups that cut across a range of obesity-related prenatal and postnatal exposures and outcomes. Examples of significant prenatal disparities include differences in parental overweight and gestational weight gain; examples of significant postnatal disparities include differences in overweight and obesity in children under the age of 5. Adair noted that the fastest growing rates of childhood obesity worldwide are in low-income groups. Adair also introduced the "mismatch hypothesis," that is, the notion that the risk of childhood obesity appears to be greatest among undernourished fetuses who are then exposed to over-nutrition postnatally. The mismatch hypothesis was revisited several times during the workshop discussions.

While most of the workshop presentations and discussion focused on the role of maternal contributors to the risk of childhood obesity, Stephen Krawetz, Wayne State University School of Medicine, shifted the focus to, in his words, what "Dad delivers." He provided an overview of the role of sperm in early development; described the many different types of RNA molecules that sperm deliver to the oocyte, including several that have been implicated as having an early developmental role in obesity; and discussed evidence indicating epigenetic-mediated transgenerational inheritance through the paternal line, affected largely by paternal nutrition.

Caroline Relton, Newcastle University, emphasized that both over-nutrition and under-nutrition during pregnancy can impact childhood adiposity. In her opinion, the evidence is compelling. The question for her is, what is the role of epigenetics? Relton stated that while identifying associations between methylation patterns

[3] DNA methylation is one of several epigenetic mechanisms. Not too many years ago it was believed that a methylated gene was a silent gene, but now it appears that sometimes DNA methylation activates genes, depending on where the gene is methylated.

and phenotypes has become straightforward, inferring causality remains a challenge. Revisiting and expanding on ideas introduced by Baccarelli, Relton laid out the steps necessary to infer causality and distinguish merely correlational findings or those due to confounding. She gave numerous examples and considered ways to improve those steps, including refined measures of maternal obesity, an increased awareness of the pitfalls of association studies, and the use of triangulation of evidence built on multiple research study design types to infer causality.

Opportunities for Intervention and Prevention

Moderated by Leann Birch, University of Georgia, Session 3 speakers discussed potential opportunities for intervention and prevention based on the rapidly advancing knowledge of the role of epigenetics and other factors in the early origins of obesity.

Reiterating what Adair and Relton had earlier voiced about the importance of not just maternal overnourishment but also maternal undernourishment in increasing the risk of childhood obesity, Lillycrop summarized animal and human data suggesting that both maternal over-nutrition and under-nutrition can cause long-term metabolic changes in offspring and that many such changes are associated with altered DNA methylation patterns. These same patterns extend into the early postnatal life as well. She echoed Baccarelli's and others' hope that in the future, DNA methylation differences at birth can be used as predictive biomarkers of later adiposity. Additionally, she speculated on the possibility of identifying stable epigenetic marks that could be used to monitor success of intervention over the course of life. But again, as with epigenetic markers at birth, several obstacles will need to be overcome and questions answered before the use of monitoring biomarkers becomes a clinical reality. For example, are the marks causal? What other epigenetic changes are occurring besides methylation? Which marks can be changed with nutritional or other intervention and if so, when and how?

Kevin Grove, Novo Nordisk, called attention to placental function and its association with a wide range of downstream metabolic complications. Based on research using a nonhuman primate model, evidence indicates that regardless of maternal BMI, a high fat maternal diet during pregnancy results in increased inflammatory cytokine production in the placenta and, upon crossing the placental barrier, in the fetus as well. Grove suggested that fetal systemic inflammation might be a potential target for therapeutic intervention. A high-fat maternal diet during pregnancy, when maintained postnatally through weaning, also has significant downstream effects on offspring neurochemistry and behavior. However, some of these effects are mitigated if postnatal nutrition has normal fat composition. Again research in nonhuman primates indicates that a prenatal and early postnatal high-fat diet causes decreased serotonin and dopamine levels in the brain as well as abnormalities in appetite-regulating neurochemistry. In terms of interventions, Grove emphasized the importance of testing any proposed intervention, whether it involves diet and exercise, surgery, or pharmacotherapy, before implementation. Results from pre-pregnancy bariatric surgery studies in rodents and humans have yielded conflicting risk–benefit results.

The perinatal period is sensitive not only to dietary fats, but also to leptin, a hormone produced by adipose cells. Marie-France Hivert, Harvard Medical School, discussed the physiology of leptin and summarized findings from animal and human observational studies suggesting that leptin exposure during the perinatal period is associated not only with early-life weight gain but also long-lasting changes in the hypothalamus and other tissues. Additional human data from Hivert's laboratory group suggest that leptin levels in offspring are regulated, at least partially, by epigenetic changes in the placenta triggered by changes in maternal glucose levels.

According to Mark Vickers, Liggins Institute at the University of Auckland, leptin was one of the first obesity interventions tested in an animal model. When results suggested that administering leptin could stop overeating in animals on high-fat diets, there were calls to add leptin to infant formula. But the effects were also shown to depend on the nutritional status of the mother and to be sex-dependent. Vickers summarized results from mostly animal obesity intervention studies testing a range of strategies from leptin to exercise. In his opinion, it is reassuring that so many different animal models, from sheep to mice, demonstrate similar reversals in metabolic dysfunction resulting from early life interventions. But researchers need to gain a better understanding of short-term versus long-term trade-offs and how to apply results from animal studies to humans.

There was a great deal of discussion throughout the workshop about the human microbiome and how gut microbial metabolites can impact infant metabolism and risk of childhood obesity. William Nierman, J. Craig Venter Institute, provided an overview of the human microbiome and efforts over the past decade to develop an awareness of its significance in human health. He remarked that microbiome metabolic capabilities supplement host metabolic capabilities, for example by digesting complex carbohydrates, with consequences for cancer and other disease phenotypes.

Meredith Hullar, Fred Hutchinson Cancer Research Center, expanded the discussion of microbiome to epigenetics and observed that researchers have moved beyond simply reporting associations between the microbiome and host epigenetic patterning and are beginning to study how microbial metabolism actually mediates the observed epigenetic changes. For example, many host genes associated with satiety are influenced by exposure to fatty acid metabolites of the gut microbiome. Although she and others have found associations between the dominant microbial make-up of the gut microbiome and adult adiposity, it is difficult at this point to conjecture how the early life microbiome affects the risk of obesity. The field is limited by small sample sizes and lack of prospective studies.

While the focus of the workshop was examining childhood obesity, several speakers advocated for thinking less about size, or BMI, and more about the metabolic dysregulation that can occur in both obese and lean individuals. It is especially helpful to think about metabolic dysregulation when thinking about the effect of obesity on the brain, Antonio Convit, Nathan Kline Institute for Psychiatric Research, opined. Convit considered how metabolic dysregulation in adolescents leads to impaired cognitive tasks and reduced hippocampal volume, with insulin resistance being the primary driver. He suggested that retinal arterial width be considered as a potentially useful biomarker for metabolic dysfunction in the brain and identified exercise and sleep, because of their known associations to improve insulin resistance and metabolic dysfunction, as two “easy public health handles” for obesity intervention in adolescents.

Real-World Application

Given the dynamism, complexity, and context-dependency of childhood obesity etiology, speakers in Session 4, moderated by Debra Haire-Joshu, Washington University in St. Louis, explored in detail some of the challenges and opportunities for real-world application.

According to Aryeh Stein, Emory University, the Dutch Hunger Winter of 1944–1945, which Lillycrop had briefly mentioned in her earlier presentation, has long been recognized by researchers as a useful period for studying the effects of short-term hunger on subsequent generations. Stein summarized evidence from those and other studies on “real world” human prenatal exposure to famine and its effects on obesity-related outcomes. In addition to the Dutch Hunger Winter and other periods of famine during WWII, researchers have examined next-generation obesity-related outcomes of the China famine of 1959–1961 and the Biafra, Nigeria, famine of 1967–1970. Stein emphasized that all of the studies he surveyed are flawed by fundamental confounding factors, the main one being that women become amenorrheic when food is restricted, so fertility drops, making it impossible to know how children born to fertile women are different than those who would have been born if fertility had not dropped. Additionally, none of the studies can separate the effects of hunger from the effects of other stressors such as the extreme cold temperatures of the Dutch Hunger Winter. That said, Stein observed two general conclusions: (1) female offspring appear to be more vulnerable to prenatal exposure than male offspring, and (2) gestational exposure appears to have a greater effect than later exposure.

Following Stein’s presentation, the focus of the workshop shifted to the social, health policy, and clinical implications of the wide range of animal and human evidence being discussed. Sarah Richardson, Harvard University, began by exploring the implications for women, particularly poor women of color, of the predominant focus on female reproductive bodies as a central site for obesity-related epigenetic programming and public health intervention. She expressed concern that, unless some critical issues are tended, the public discourse around epigenetics and obesity is likely to become deterministic and stigmatizing in a way that threatens women’s reproductive autonomy. When communicating about epigenetic science in the public sphere, she urged greater

emphasis on the complexity of the science, differences between animal and human studies, the role of paternal as well as maternal effects, and the need to seek societal changes rather than individual solutions.

In his discussion of the role of scientific evidence in Developmental Origins of Health and Disease (DOHaD) health policy development and implementation, Gillman agreed with Stein that obesity prevention calls for a greater focus on the environment and policy and less emphasis on the individual. He emphasized the importance of evidence in policy decision making and identified ways to improve DOHaD etiological evidence from both animal and human studies. He urged researchers who rely on animal models to harmonize experimental designs, allowing for a more bidirectional approach to how animal and human researchers work together to inform their research questions to enhance translational relevance. He also encouraged increased publications on null results. He suggested that more innovative experimental designs and analyses and greater comparing and contrasting across studies could help to overcome the confounding limitations of human observational research. He also discussed how prediction models, risk/benefit and intervention studies, long-term simulation modeling, and natural evaluation experiments can help to inform DOHaD policy.

Finally, Barkin brought the discussion full circle by reiterating what Hassink had emphasized in her opening remarks, that is, the clinic setting as a ripe environment for implementing childhood obesity interventions. The challenge is, how? Based on recent research, Barkin identified several potential clinical interventions to prevent childhood obesity and metabolic dysfunction. For example, evidence suggests that poor maternal nutrition during pregnancy combined with rapid infant catch-up growth leads to increased and metabolic dysfunction in offspring. A potential clinical application of this knowledge is the promotion of appetite regulation during infancy. But again, how? One of the objectives of the Greenlight Intervention Study, according to Barkin, is to develop methods for training providers to teach parents how to recognize hunger and satiety cues in their infants and how to soothe infants in ways that do not only rely on feeding. Based on results from multiple studies, Barkin suggested several interventions that can be implemented in clinical settings, such as (1) providing group visits or health coaching calls to pregnant women to maximize appropriate nutrition and gestational weight gain and during the post-pregnancy period to support appropriate weight loss after delivery, and (2) delivering behavioral interventions focused on families rather than on children.

Data Gaps and Future Directions

To conclude the workshop, first, Esa Davis, University of Pittsburgh Medical Center, moderated a discussion with workshop speakers on possible future research directions with an emphasis on expanding what scientists know about epigenetic-mediated associations between early developmental exposures and subsequent obesity-related health outcomes. The first discussion with the workshop speakers was moderated by Davis and summarized the workshop themes. The second discussion was moderated by Judith Hall, University of British Columbia, who facilitated participants and audience member questions. Key points from both discussions are summarized here. Much of the discussion revolved around how to strengthen human observational studies in ways that will allow researchers to extract more types of useful information about the mediating role of epigenetics, especially given that many existing study cohorts were developed before epigenetics was consistently considered. Several workshop participants called for more cohorts from countries in transition (the Global South). Most existing cohorts are in developed countries (the Global North), representing only a portion of the variation in exposures and outcomes that likely exists among populations. Regardless of the population studied, with respect to the types of exposure data needed, echoing earlier calls for a greater focus on paternal contributions to metabolic dysfunction in early childhood, several participants emphasized the need to collect paternal behavioral and biological information. There was also some discussion about how best to measure nutritional exposure, especially during pregnancy, in order to gain a better understanding of how not only maternal but also placental and fetal dietary exposure impacts obesity-related outcomes. With respect to the types of outcome data needed, many participants agreed that researchers should rely less on BMI and consider more precise outcome measures of obesity, body composition, and metabolic dysfunction.

In terms of how to improve the collection of epigenetic data that may be predictive of exposure-outcome associations, given the tissue- and cell-specificity of epigenetic patterning, several participants agreed with the need for more careful tissue selection, that is, sampling based not only on convenience but also on the nature of the question being asked. A number of participants also mentioned the need to collect genetic alongside epigenetic data so that epigenetic variation can be viewed within the context of genetic variation.

Given that more epigenetic data will be collected in the future and that as more data are collected, the complexity of the datasets will likely expand, a participant asked: Is there enough computing power to accurately predict likely biological outcomes based on those data? Several others agreed that computing power is not the limitation. Rather, the challenge will be to make sense of the data. One participant speculated that teams of scientists will need to be assembled to interpret the data. Another wondered if a systems science approach may be helpful.

In her concluding remarks, Barkin reiterated that epigenetics is only one of several potential mechanisms mediating the dynamic relationship between early exposure and the development of childhood obesity. That said, the opportunities to apply what scientists are learning about epigenetics, in the context of the developing child and obesity, are vast. "The potential power of epigenetic science," she said, "is understanding what we can do today to affect the health of future generations as well as what we can do today to mitigate or modify the effects on this generation."

PLANNING COMMITTEE ON UNDERSTANDING THE DYNAMIC RELATIONSHIP BETWEEN BIOLOGY, ENVIRONMENT, AND EARLY CHILDHOOD DEVELOPMENT ON RISK OF OBESITY*

Shari Barkin, Monroe Carell Jr. Children's Hospital at Vanderbilt University; **Leann L. Birch,** University of Georgia; **Esa Davis,** University of Pittsburgh Medical Center; **Stephen R. Daniels,** University of Colorado School of Medicine; **Matthew W. Gillman,** Harvard School of Public Health; **Debra Haire-Joshu,** Washington University in St. Louis; and **Karen A. Lillycrop,** University of Southampton.

*IOM planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published Workshop in Brief rests with the institution.

DISCLAIMER: This workshop in brief has been prepared by **Leslie A. Pray,** rapporteur, as a factual summary of what occurred at the meeting. The statements made are those of the authors or individual meeting participants and do not necessarily represent the views of all meeting participants, the planning committee, or the National Academies.

REVIEWERS: To ensure that it meets institutional standards for quality and objectivity, this workshop in brief was reviewed by **John G. Kral,** SUNY Downstate Medical Center, and **Charlotte A. Pratt,** National Institutes of Health. **Chelsea Frakes,** Institute of Medicine, served as review coordinator.

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For additional information regarding the workshop, visit www.iom.edu/fetaldevelopment.