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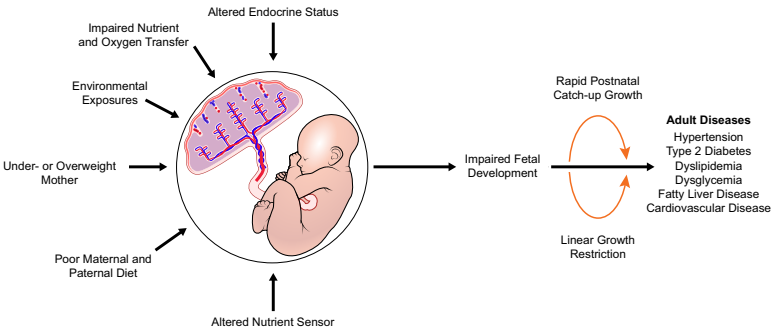
REVIEW ARTICLE

DEVELOPMENTAL ORIGINS OF METABOLIC DISEASES



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KEY WORDS

developmental origins; environmental toxins; metabolic diseases; obesity; placenta

CLINICAL HIGHLIGHTS

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2. Poor growth in utero or during early childhood has also been shown to result in adapted metabolism and altered body composition that may increase the risk for chronic diseases in adulthood.
3. Numerous epidemiological and animal studies have further elucidated Barker's early work and explain how placental-induced IUGR manifests in dysglycemia, dyslipidemia, fatty liver disease, and adverse cardiovascular outcomes.
4. As the interface between the mother and her developing infant, the placenta is actively responding to a wide variety of maternal signals and changing its function according to the ability of the mother to support fetal growth and development.
5. Metabolism disrupting chemicals are ubiquitous in the modern environment, and exposure (in utero or postnatally) may compound the impacts of an adverse in utero environment and promote metabolic disease.

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REVIEW ARTICLE

DEVELOPMENTAL ORIGINS OF METABOLIC DISEASES

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Abstract

Almost 2 billion adults in the world are overweight, and more than half of them are classified as obese, while nearly one-third of children globally experience poor growth and development. Given the vast amount of knowledge that has been gleaned from decades of research on growth and development, a number of questions remain as to why the world is now in the midst of a global epidemic of obesity accompanied by the "double burden of malnutrition," where overweight coexists with underweight and micronutrient deficiencies. This challenge to the human condition can be attributed to nutritional and environmental exposures during pregnancy that may program a fetus to have a higher risk of chronic diseases in adulthood. To explore this concept, frequently called the developmental origins of health and disease (DOHaD), this review considers a host of factors and physiological mechanisms that drive a fetus or child toward a higher risk of obesity, fatty liver disease, hypertension, and/or type 2 diabetes (T2D). To that end, this review explores the epidemiology of DOHaD with discussions focused on adaptations to human energetics, placental development, dysmetabolism, and key environmental exposures that act to promote chronic diseases in adulthood. These areas are complementary and additive in understanding how providing the best conditions for optimal growth can create the best possible conditions for lifelong health. Moreover, understanding both physiological as well as epigenetic and molecular mechanisms for DOHaD is vital to most fully address the global issues of obesity and other chronic diseases.

developmental origins; environmental toxins; metabolic diseases; obesity; placenta

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CLINICAL HIGHLIGHTS

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4. As the interface between the mother and her developing infant, the placenta is actively responding to a wide variety of maternal signals and changing its function according to the ability of the mother to support fetal growth and development.
5. Metabolism disrupting chemicals are ubiquitous in the modern environment, and exposure (in utero or postnatally) may compound the impacts of an adverse in utero environment and promote metabolic disease.

1. EPIDEMIOLOGY OF THE DEVELOPMENTAL ORIGINS OF ADULT HEALTH AND DISEASE

1.1. Introduction

For perhaps the first time in modern history, the height of US Americans appears to have reached a plateau (1), while a generation of children in Japan may not grow taller than their parents. A recent study in *Scientific Reports* described a trend in Japan in which pregnant women are gaining less weight than recommended, a phenomenon that is accompanied by an increased prevalence of low-birth-weight babies and a mean adult height that has been decreasing by a few millimeters a

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year since the mid-1990s (2). Although some may suggest that this is nothing more than a natural variation in body size, a "fetal programming" perspective predicts that Japan may witness a concomitant increase in the incidence of nutrition-related chronic diseases in coming years. The reasoning for such an assertion rests with the evidence available from research on the long-term influence of nutrition and growth during gestation on adult health, broadly known as the "developmental origins of health and disease" or DOHaD.

The historical origins of DOHaD date back to research on mortality rates in England and Wales in which David Barker and colleagues (3) reported that men were dying from diseases normally associated with wealth but in regions of relative poverty with a high prevalence of low birth weight. From available ecological data on infant mortality rates and deaths from diseases in England, there was a high correlation (0.79–0.83) between infant mortality from 1921 to 1925 and deaths from heart disease, bronchitis, and stomach cancer from 1968 to 1978 and a low correlation (0.46–0.54) with lung cancer and stroke, with some variations in degree of correlation by sex and age. However, the authors were extremely cautious in their conclusions and cited a number of similar studies that found consistent trends but did not rule out confounding factors that could not be included at the time because of either lack of data or statistical methods that were unable to control for confounding variables. Still, since that publication in 1986, there are now over 1,000 scientific papers on the topic "developmental origins of health and disease."

To best illustrate how windows of opportunity exist to either promote health or increase the risk of disease, it is essential to consider those factors that support human growth and development even well in advance of conception. Given that the intrauterine period is one of tremendous cellular growth and differentiation, a brief review of how maternal diet influences fetal growth is provided. *Preconception and Early Life Influences on Growth* complements a more in-depth discussion of current research of placental influences on fetal growth and offspring health presented in subsequent sections of this article. As well, understanding the confluence of dietary and environmental factors as they interact to support fetal growth is essential to developing a broad appreciation of the multitude of factors related to "fetal programming" as depicted in **FIGURE 1**.

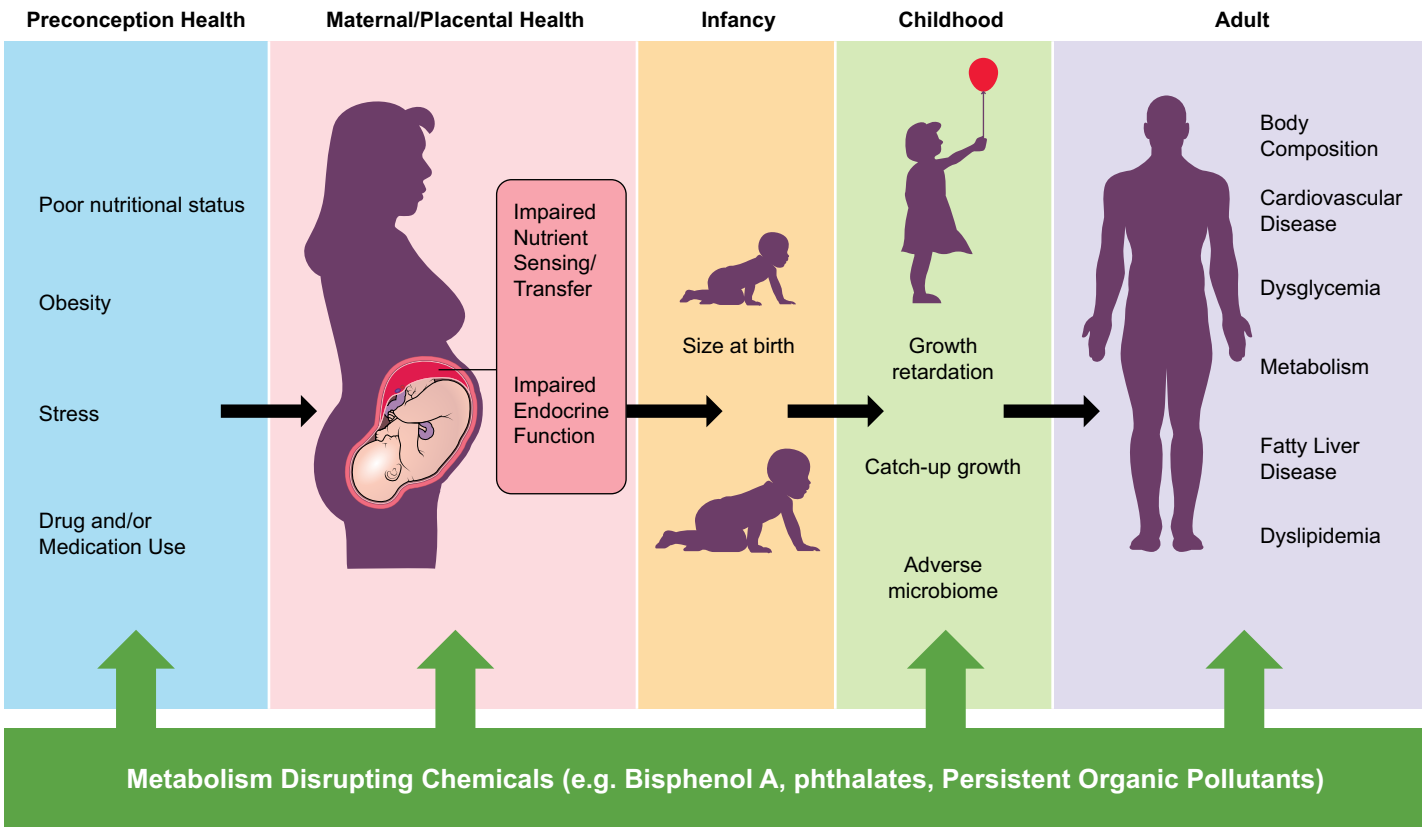

FIGURE 1. Schematic of potential preconception and maternal/placental health factors that can influence birth size and the impact on health in childhood that can influence adult health in the long term with underlying environmental disruptors that contribute to the developmental origins of metabolic diseases.

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1.2. Preconception and Early Life Influences on Growth

An increasing number of studies have shown that paternal and maternal body composition and diet influence not only the first generation of offspring (4–6) but the second generation as well (7). Moreover, some studies are now reporting not only phenotypic differences in children exposed to poor maternal or early childhood diet but also epigenetic differences that provide mechanistic hypotheses (8). The intrauterine period of growth is extremely important for lifelong health, as growth and development of fetal tissues and organ systems occur at a very rapid pace. Any perturbation to this process, through either nutritional insufficiency or exposure to endocrine disruptors or toxicants (discussed in detail in IN UTERO ENVIRONMENTAL CHEMICALS AND METABOLIC DISEASES), not only interrupts or delays the growth process but may be manifested as metabolic abnormalities that challenge adult health. Indeed, altered growth patterns, such as slow or rapid growth, are now considered to be a primary predictor of body composition and health. However, it is helpful to provide a brief overview of major factors that affect both intrauterine and postnatal growth before discussing the intricacies of DOHaD. More important, within this section, but more so in subsequent sections, specific physiological mechanisms that underlie epidemiological or clinical studies are reviewed in great detail to fully explore how perturbations to normal growth and development increase the risk of chronic diseases later in life.

1.2.1. Maternal diet and nutritional status.

The influence of maternal diet and nutritional status on fetal growth and health of the offspring is well documented in other reviews (9, 10), but it is important to consider that a host of other factors also influence fetal growth, such as maternal smoking, which explains 52% of the variance in birth weight and 37% of the variance in birth length (11). With respect to maternal diet, a number of studies have been conducted to investigate the relationship between maternal diet and birth weight. For example, one study of maternal factors used path analysis to determine the interactions between maternal dietary patterns and maternal cytokines on birth weight and determined that a maternal diet composed primarily of tubers and eggs is associated with low birth weight, mediated by high maternal adiponectin concentrations (12). A study from Brazil reported that a dietary pattern defined as "highly processed," based on maternal dietary records showing a greater intake of refined grains, high-fat foods, and low fiber, increased the risk of delivering a small-for-gestational age (SGA, birth weight below the 10th percentile of a reference) baby (13). Likewise in a study of 1,040 women in the United States, poor maternal dietary quality, based on a low score of the Healthy Eating Index (HEI), as well as a high-fat diet were associated with increased neonatal adiposity but not lean body mass (LBM) (14, 15). In Nepal, maternal supplementation with folic acid, iron, and zinc resulted in children having lower fat mass (FM) compared with children born to control mothers (16). As well, a higher maternal intake of n–3 and n–6 fatty acids was associated with greater adiposity assessed by skinfold measures at the age of 3 yr (17). With regard to maternal body composition, a small cohort study from Brazil reported that maternal FM was predictive of birth weight and fetal growth, independent of diet (18). Thus, improving maternal health and ensuring a minimum level of food security and dietary diversity to all mothers must be a priority for health professionals throughout the world. In short, improving maternal nutrition is among the best means to prevent acute and chronic diseases of their children.

Although dietary intake is difficult to assess in free-living people, a great deal of knowledge can be gleaned from randomized controlled trials in which women receive a nutritional supplement or a placebo. Such studies are the best approach to determine how a nutrient or combination of nutrients can influence fetal growth and offspring health, independent of potential confounding factors. For example, offspring of women who used multivitamins during pregnancy had a slower rate of FM accretion compared with offspring of control women (19). Regarding bone density, increased maternal intake of calcium-rich food and higher folate status are associated with greater offspring bone mineral content (BMC) and bone mineral density (20). It has also been found that higher first-trimester vitamin B_{12} status is associated with greater BMC, adjusted for total bone area (21). Finally, maternal β-carotene concentrations were associated with greater offspring BMC at 2 wk postnatal (22). Potential mechanisms for these observations include epigenetic modifications that may promote adiposity, as it has been reported that hypermethylation of the umbilical cord tissue retinoic acid X receptor, a key regulator of adipocyte proliferation, was associated with increased offspring FM at 9 yr of age (23). However, there is an overall lack of consistent and robust data on the influence of maternal micronutrient intake on body composition in childhood. It is important to note that one would not expect to detect significant differences between groups <1 yr of age given that development of adipose tissue is highest during the first postnatal year, with a second period of rapid adipose tissue deposition in the prepubertal period (9–14 yr) (24).

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1.2.2. Maternal obesity and offspring health.

Given the increased global prevalence of obesity (25), the impact of maternal obesity on fetal development and offspring health has gained tremendous attention over the past 20–30 yr. Although this topic has been explored previously (26), it merits a brief discussion given that the mechanisms related to placental influences on fetal health as well as maternal physiology and later offspring health are discussed below in this review. A recent meta-analysis of a large number of birth cohorts found that a higher maternal prepregnancy body mass index [BMI, weight (kg)/height (m)^2] increased the risk of the offspring being overweight (6). Specifically, a child born to a woman with a prepregnancy BMI $>$ 25 was 1.7 times more likely to be overweight in early childhood and twice as likely to be overweight in late childhood. The authors also reported that greater gestational weight gain increased the risk of childhood overweight, independent of prepregnancy BMI. Although BMI is only a clinical indicator of excess adiposity, a study of 24,289 offspring from the Nurses' Health Study II found that children born to women who were obese had higher percent body fat, systolic blood pressure, and fasting glucose at ages 9–14 yr compared with offspring of normal-weight women, despite having similar birth weight and despite statistical adjustment for lifestyle factors that may promote obesity (27). Yet the precise mechanisms underlying these associations are poorly understood given the multitude of factors that influence not only fetal development but adult health, given the diverse environmental changes that occur after birth and well into adulthood.

A number of studies of both humans and rodents do provide insight into potential physiological mechanisms that explain how maternal obesity may promote poor health outcomes for offspring later in life. For example, one study found that offspring telomere length decreased as maternal BMI increased even after adjusting for maternal education, maternal and paternal age, and birth weight (28). Higher maternal BMI was also negatively associated with cord blood and placental telomere length, suggesting that a higher maternal BMI may influence cellular functions of the placenta well before any negative health outcomes are manifested in the offspring (discussed in greater detail in ROLE OF THE PLACENTA IN FETAL GROWTH AND METABOLIC DISEASES). In a study of obese female mice, not only were the offspring more hyperinsulinemic compared with control pups, but they also presented with increased hepatic lipid content, increased concentrations of peroxisome proliferator-activated receptor (PPAR)γ, and lower concentrations of triglyceride lipase (29). It was suggested that these findings could be attributed to altered mitochondrial function as evidenced by uncoupling of the cytochrome system and increased hepatic oxidative stress as a result of insulin resistance and subsequent effects on the regulation of hepatic lipid metabolism. The results of this study are consistent with another study of rats in which pups born to obese mothers had similar lipid profiles and insulin resistance (30). When the authors studied differential gene expression with RNA-sequencing analyses, it was determined that 1,365 genes in the male offspring and 70 genes in the female offspring were expressed differently from control offspring and that most of the altered genes were essential for insulin signaling and lipid metabolism. Finally, one study of note focused on the long-term effects of maternal obesity in baboons, where female baboons were fed a high-fat, high-fructose diet before conception (31). It was found that offspring of the high-fat baboons, compared with control offspring, had higher hepatic lipid accumulation and downregulation of genes associated with the tricarboxylic acid (TCA) cycle and oxidative phosphorylation pathways. More explicit mechanisms beyond those discussed focused on epigenetic changes that may be attributed to maternal obesity and are discussed in subsequent sections below.

1.2.3. Breastfeeding and complementary feeding.

From the moment of birth, the newborn is dependent on others for providing energy and nutrients, and breastfeeding is the best method for ensuring healthy growth and development (32). However, $<$12 mo of exclusive breastfeeding is associated with $>$800,000 deaths in children under 5 yr of age (33). Still, in many low-income countries, fewer than 50% of newborns are breastfed and only 41% are exclusively breastfed in the first 6 mo (34). Among breastfed babies, the metabolically active lean tissue mass almost doubles and the primary source of energy provided is still from breast milk, but after 6 mo of age, energy from breast milk gradually becomes insufficient to meet the increased energy needs of the infant. Therefore, the difference between energy delivered and energy required to maintain homeostasis and growth must be met by solid foods, known as complementary foods. Any delay in the delivery of complementary foods or providing less than optimal nutrition slows or halts growth, as energy and nutrient needs are unmet during this period of rapid growth. The introduction of optimal complementary foods beginning at 6 mo of age is important, along with ensuring that such foods are age appropriate, safely prepared, and of good quality to prevent deficiencies or other food-borne illnesses that can interrupt healthy growth. Regardless, it is estimated that $<$25% of children under the age of 2 yr in low- and middle-income countries receive foods from the

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recommended food sources (i.e., dairy, fruits and vegetables, and protein sources) and almost 30% of children under 1 yr of age do not receive any complementary foods, a major and serious threat to their growth and future health (35).

1.2.4. Intestinal disruptions and microbiome.

The delivery of nutrients to any animal occurs through absorption in the intestines. Changes to cellular structure, mucosal composition, or bacterial population of the intestines threaten this process and can result in growth deficits. Enteropathogenic bacteria that cause diarrhea are known to change the cytoskeletal arrangement of enterocytes, essentially breaking down the normal intestinal barriers, limiting complete absorption of nutrients (34). In fact, the number of episodes of diarrhea is positively associated with postnatal growth retardation (36), and the more often a child suffered diarrhea before age 2 yr, the more likely he/she is to experience growth retardation. The implications of these findings are great given that intestinal infections and enteropathy are highly prevalent and caused by a myriad of factors that are not nutritional in nature but have a direct impact on nutritional status, regardless of the diet consumed. Along with the impact on nutritional status is the ongoing issue of how infections affect the microbial milieu of the intestines, namely the microbiome (37).

The microbiome has gained a lot of attention in the past decade, particularly as new research has shown that specific profiles of the microbiome predict childhood obesity and body composition (38, 39). One study from Madagascar found that stunted children [height for age *z* score (HAZ) less than −2.00] presented with intestinal bacterial overgrowth composed of bacteria that are more consistent with the oropharyngeal cavity (40). The authors concluded that the conditions that precipitated growth retardation were accompanied by a "decompartmentalization" of the gastrointestinal microbiome in which the normal intestinal milieu is replaced by oropharyngeal bacteria from the stomach to the colon. Furthermore, undernourished children have a poorly developed gut microbiota (41), which is important for growth given that bacterial β-fructofuranosidases cleave β(2,1) bonds differentially in sucrose, fructooligosaccharides, and inulin (44). Moreover, gut microbiota assist in the digestion of nonresistant starch (45) and are capable of producing amino acids (46) and some B vitamins (47, 48), suggesting that the microbial profile plays an important role in healthy growth and may prevent growth faltering.

Several studies have now investigated the relationship between the microbiome and growth retardation. One of the most elegant studies to date was conducted in Bangladesh, in which a healthy microbial profile was established as a reference (49). It was found that children with subacute malnutrition presented with an "immature" microbiome relative to the reference and that this profile became more consistent with the reference after treatment with either a standard therapeutic diet (Plumpy'Nut) or khichuri-halwa, a local therapeutic diet composed of rice, lentils, green leafy vegetables, and oil. This work is complemented by a clinical study in which bacteria from undernourished children was transplanted to germ-free mice and the immature microbiota from the undernourished children resulted in impaired growth of the otherwise healthy mice that were fed a standard diet (50). Taking this research even further, a randomized, double-blind protocol was used to compare standard therapy with various microbiota-directed complementary food (MDCF) prototypes in Bangladeshi children with moderate malnutrition (51). The MDCF group had increased concentrations of insulin-like growth factor binding protein (IGFBP)-3 and decreased concentrations of growth differentiation factor 15, growth and bone formation promoter and agonist, respectively, similar to what was observed in healthy children. Thus, diet and the microbiome not only are critical for supporting healthy growth but appear to interact at a highly refined level to promote growth when conditions are favorable.

Part of the mechanism behind how the microbiome promotes or impedes growth may be through the role of various bacterial phyla on proper functioning of metabolic pathways. For example, the Bacteroidetes phylum is richer in genomes central to biosynthesis of biotin, folate, riboflavin, and de novo niacin synthesis compared with Firmicutes. In addition, almost all Bacteroidetes species are able to synthesize pantothenic acid, coenzyme A (CoA), and thiamine monophosphate, essential nutrients for the tricarboxylic acid (TCA) cycle and for metabolism of fatty acids, as CoA is essential to activate fatty acids (as acyl-CoA) for β-oxidation. Importantly, these B vitamins are necessary for energy metabolism and are required for proper functioning of the metabolic pathways for glucose metabolism and β-oxidation. Moreover, biotin is a cofactor for converting propionyl CoA to methylmalonyl CoA, which enters the TCA cycle as succinyl CoA and allows some amino acids (e.g., isoleucine and methionine) to enter the TCA cycle. The final step of the process requires vitamin B_{12} and folate, which are essential for the pathway to continue to produce ATP and without which the metabolic capacity of the cells is compromised.

Within the context of DOHaD, a number of areas of opportunity exist in which perturbations to maternal health, through either nutritional deficiencies or excesses, may have a significant impact on fetal growth and development. To further illustrate such effects, a review of famine

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studies and birth cohorts along with clinical studies of poor childhood growth is presented below.

1.3. Cohort Studies of Development Origins of Metabolic Diseases

Although DOHaD is a relatively broad field, there are a number of population studies that have demonstrated an increased risk of obesity and other chronic diseases in children born after in utero nutritional insults. Moreover, analyses of data from famines and historical cohort studies have provided some of the most consistent and compelling data on this topic. More recently, clinical studies of adults and children who experience nutrient or energy restriction during gestation and early life are now providing exciting new data on physiological adaptations following growth retardation. The studies reviewed below draw from a diversity of cohorts, including survivors of famines and recent experiences of migrating refugees. The precise physiological modifications or adaptations that can explain or support these epidemiological or clinical studies are further explored in subsequent sections on placental, molecular, and environmental mechanisms of DOHaD.

1.3.1. Famine studies.

Famines throughout the world have occurred for a variety of reasons (e.g., civil strife, war, political instability, climate change), and a number have been studied retrospectively to understand the influence of famine on in utero and postnatal growth and subsequent adult health as presented in a number of books and reviews (52, 53). For brevity, this review focuses on just two of the most well-studied famines. One of the first cohort studies of in utero famine exposure and adult health is the Dutch Hunger Winter study of adults who were born before, during, and after the Nazi-imposed famine of 1945–46, during which time pregnant women consumed between 750 and 1,000 calories per day (54). Using birth records, investigators identified adults who were exposed to the famine during specific periods of gestation and categorized them according to early, middle, or late gestation. Health outcomes among these famine-exposed individuals have been extensively compared to outcomes among adults born before the famine or conceived after the famine. Those adults (mean age of 29 yr) who were exposed to maternal starvation in late gestation had lower glucose tolerance compared with those exposed early in gestation or never exposed to the famine (54). In addition, adults who were exposed to the famine during any 10-wk period of gestation had an increased risk for hypertension compared with unexposed adults (55). Likewise, poor growth due to undernutrition or micronutrient deficiencies has been found to increase the risk of obesity (56, 57), and men from the Dutch famine cohort who were exposed to famine during the first two trimesters of gestation had a higher risk of obesity compared with men exposed during late gestation and early infancy (58).

A second well-characterized famine cohort comprises adults who were born during the Chinese "Great Famine" of 1959–1961 (52), a famine that lasted far longer than the Dutch famine and affected millions of adults and children. Adults at 56 yr of age who were exposed to the Chinese famine in utero were 1.5 times more likely to develop T2D compared with unexposed adults (59). Similar to the Dutch Hunger Winter study, adults exposed to the Chinese famine in utero had a fourfold greater risk of hypertension compared with unexposed adults at age 32 yr (60). As well, women who were exposed to the Chinese famine in utero were more likely to be obese compared with women born after the famine (61). To address how famine exposure in utero interacts with broad dietary changes, adult survivors of the Chinese famine were included in a clinical study of T2D and dietary intake and analyzed by famine exposure and diet (62). Adults who had been exposed to severely affected famine areas in utero were more likely to have hyperglycemia compared with nonexposed adults, yet those adults who had been exposed to severe famine in utero and consumed a "Western" diet were almost eight times more likely to have hyperglycemia compared with the nonexposed adults. This study may be among the first that clearly showed not only how in utero nutrient deprivation has long-term metabolic consequence but that such perturbations are exacerbated by environmental changes, such as shifts from a traditional to a Western diet, and is a clear demonstration of how the prenatal and postnatal environment may interact and impact the risk of chronic diseases.

1.3.2. Historical cohort studies.

Perhaps one of the best-studied birth cohorts of healthy children is the Hertfordshire cohort, in which >1,000 babies were included in a program that recorded birth weight and early feeding practices beginning in the 1920s (63). From this cohort, close to 265 studies have been conducted, with hundreds of papers published on topics ranging from obesity to insulin resistance to hypertension. Early studies of the Hertfordshire cohort found that term infants with a low birth weight were twice as likely to develop T2D and coronary heart disease compared with those with normal birth weight (63–65). Similar results have been published in birth cohorts from South Africa, Finland, the United States, and Brazil among others (61, 66–69). Certain inherent challenges

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exist in human cohort studies that make comparisons between them difficult and often limit consensus, such as whether or not gestational age was recorded, lack of explicit data on maternal diet or weight gain, limited access to accurate measures of body composition or infant diet, and so forth. Nonetheless, many studies have provided generally consistent results, and these studies are reviewed separately, with a discussion on the collective conclusion to follow.

To determine how socio-environmental factors influence growth, an innovative study was developed in South Africa before the fall of apartheid: the Birth to 20 (Bt20) cohort studied 3,200 infants in Soweto, Johannesburg, South Africa (67). With serial measures of body composition, postnatal growth patterns differentiated between birth size and/or growth as a risk factor for later outcomes, such as obesity. One of the most important papers published from this study found that rapid growth in infancy was associated with adolescent obesity (70). Likewise, prepubertal rapid weight gain increased the risk of adult adiposity and early menarche, a known risk factor for metabolic disorders and cancer (71, 72). Yet a cohort study in the United States found that children who experienced intrauterine growth retardation had a greater waist circumference and insulin resistance compared with children born with normal birth weight, independent of changes in BMI *z* score (BMIZ, defined as BMI relative to age according to WHO standards) from birth to age 10 yr (73). Similar results were reported for a separate study, in which children with greater childhood weight gain had greater FM, independent of birth weight, compared with children with a slower rate of weight gain (73). In short, these studies emphasized that research needs to extend beyond simple measures of fetal growth (i.e., size at birth) and childhood body size. Investigators also need to begin to explore the interactions between intrauterine growth and environmental exposures that may influence both pre- and postnatal growth, as the life course approach to both epidemiology and biology is more informative from both practical and scientific perspectives.

Exactly how postnatal growth influences nutritional status was the focus of the Project Viva study, in which a gain in BMIZ was associated with increased adiposity, independent of birth size (68). Moreover, a rapid increase in BMIZ from 6 mo to 1 yr was associated with greater insulin resistance in midchildhood (7–11 yr of age), independent of birth weight (68). As well, increased BMIZ in the first 6 mo was associated with higher systolic blood pressure in childhood (68). Thus, accelerated rate of growth, as measured by temporal changes in BMIZ, is associated with negative health outcomes later in life. This point is highlighted in a recent study of Mexican children who grew slowly, regardless of their birth size or current height, and were more likely to have greater adiposity compared with children who grew rapidly (74). Increased adiposity, although not a disease in and of itself, is associated with greater disease risk, and children who were born small with subsequent rapid growth had a greater risk for insulin resistance compared with children born larger or with a moderate rate of postnatal growth (75). Moreover, childhood obesity is a major contributor to adult obesity and poor health, suggesting that increased adiposity in childhood may increase the risk for adult obesity and chronic diseases. Clearly, nutrition during gestation has a profound and long-term impact on body size and body fat distribution and may limit the development of metabolically active tissue, contributing to metabolic disorders. Yet, as a number of different methods to assess body composition were used in the studies discussed above, along with different statistical analyses, an important point for future studies is to normalize methods to make all data comparable in terms of interpretations and comparisons of conclusions.

1.3.3. Conflicts and refugees and DOHaD.

Although global migration, in particular the migration of refugees from various conflicts and civil strife, is quite high and has gained tremendous media attention, little research on the health of such migrants has been reported. However, international migration could be a major concern to host countries, as welcoming thousands of refugees who have experienced continued nutritional and emotional challenges and are then introduced to a completely different nutritional and social environment may allow for elements of DOHaD to be expressed and result in an increased incidence of nutrition-related chronic diseases among refugee immigrants.

The issue of immigrant and refugee health becomes even more relevant to DOHaD when studies of refugee children are reviewed, given that refugees tend to experience more negative environments before emigrating compared with nonrefugee immigrants. For example, refugee immigrant children were almost five times as likely to be stunted compared with nonrefugee immigrant children (76), suggesting that refugees experience chronic undernutrition or exposure to unhealthy environments before their migration to more developed countries. These findings are consistent with another study in which 30% of refugee children were found to be growth retarded (77). One study of Sudanese refugee children reported that 30% of the children had low BMC and elevated cholesterol, triglycerides, and insulin resistance (78). The precise causes of these conditions are difficult to determine given the multitude of psychosocial and nutritional stressors faced by refugees, but given that

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almost 40% experience past and current food insecurity, dietary intake and quality are most likely important factors to consider. The height for age of the children improved during a 5-yr follow-up period, and there was a significant increase in the BMIZ as well, but not to the point of being overweight or obese. The issue of obesity is a general concern and highlights why cases of refugee migration may contribute to the prevalence of chronic diseases. In a case-control study in the United States, 512 refugee children from a number of countries were compared to 1,175 low-income US children receiving services at the same health centers (79). The refugee group had a significantly higher increase in BMIZ compared to the "control" group over a 1-yr period, and the increase was even greater for children under 2 yr of age. Moreover, refugee children who were classified as stunted had a significant increase in BMIZ, while the control children experienced a decrease during the same time period. Finally, refugee children grew from the 47th percentile of BMI, adjusted for age and sex, to the 63rd percentile, and the prevalence of obesity more than doubled in a 3-yr period. These data are important, but they must be considered with the utmost caution, as migration is a politically and socially sensitive issue. Discussing such research within the context of DOHaD is highly relevant, as understanding how nutritional and environmental insults influence lifelong health is important not just from a scientific perspective but also from the perspective of conducting research to improve the human condition, which applies to all humans, not just those who live in developed and stable countries and societies. However, there is a risk that discussion of these issues in light of recent political changes in the world may be used as an argument against migration and the hosting of refugees. Regardless, the more attention that can be devoted to understanding the health of all people may open the door for broader discussions on how to end the causes of mass migration and promote improved health and nutrition programs in situations where civil strife and unrest necessitate the migration of people.

1.3.4. Clinical studies of growth retardation and growth patterns.

Although famine studies and retrospective studies provide valuable data, more explicit information on potential mechanisms can be better gleaned from clinical studies of poor growth and biological outcomes. For example, children born small have an increased risk for obesity that is part of a U-shaped relationship between birth weight and BMI such that adults born weighing <2,500 g or >3,500 g are more likely to be classified as obese compared with those born weighing 3,000 g (80). In a study of 18,000 Swedish women, those born small or large (<2,500 g or ≥4,000 g) had a higher BMI in adulthood than women born with a "normal" weight (81). A major limitation to these studies is the use of BMI to assess obesity, as BMI is a tool for screening individuals for obesity, not a proxy for body fatness. Clinical studies that assess body composition and body fat distribution are often more helpful in elucidating the effect of early nutrition on adult body composition. It is also well recognized that birth size reflects only one dimension of growth and the postnatal period may play an equal, if not greater, role in overall growth and adult health such that the rate of growth, assessed as change in BMIZ or rate of weight gain, is predictive of adult BMI or body composition (82).

There has been considerable interest surrounding the relationship between severe growth retardation and the long-term impact on health. It was previously reported that adults who were classified as stunted (HAZ less than −2.00) are more likely to be obese compared with nonstunted peers (83). Senegalese girls who were stunted in early childhood (6–18 mo of age) had greater subcutaneous fat on the trunk and arms compared with nonstunted girls (84). Guatemalan adults who were stunted in childhood have greater central fat compared with adults who were never stunted (85), similar to stunted children in Brazil who gained more truncal fat compared with nonstunted children from the same shantytowns (86). In contrast, in the Bt20 cohort adolescents who were stunted at age 2 yr did not have a higher BMI compared with those who had never been stunted (87). It is important to note that the children in the Bt20 cohort were not classified as stunted at the time BMI was measured and many of the children could have experienced catch-up growth in the 10+ yr of follow-up. As well, a study in Bolivia found that stunted children were more likely to have a lower BMIZ and body fatness compared with nonstunted peers (88). However, no difference between height for age and FM was reported from a cohort study in Brazil (89). There are a number of reasons for what appear to be divergent results, including sample size, socio-economic environment, dietary intake, and methods to assess adiposity. The lack of consensus between various studies highlights the need to incorporate advanced imaging and statistical methods in new cohort studies and to standardize methodologies so that results between studies are comparable and available for pooled data sets that will expand the ability to address fundamental questions regarding early-life nutrition and adult health.

1.4. Physiological Adaptations following Growth Retardation

Although epidemiological studies provide solid evidence for associations and often explain how various factors

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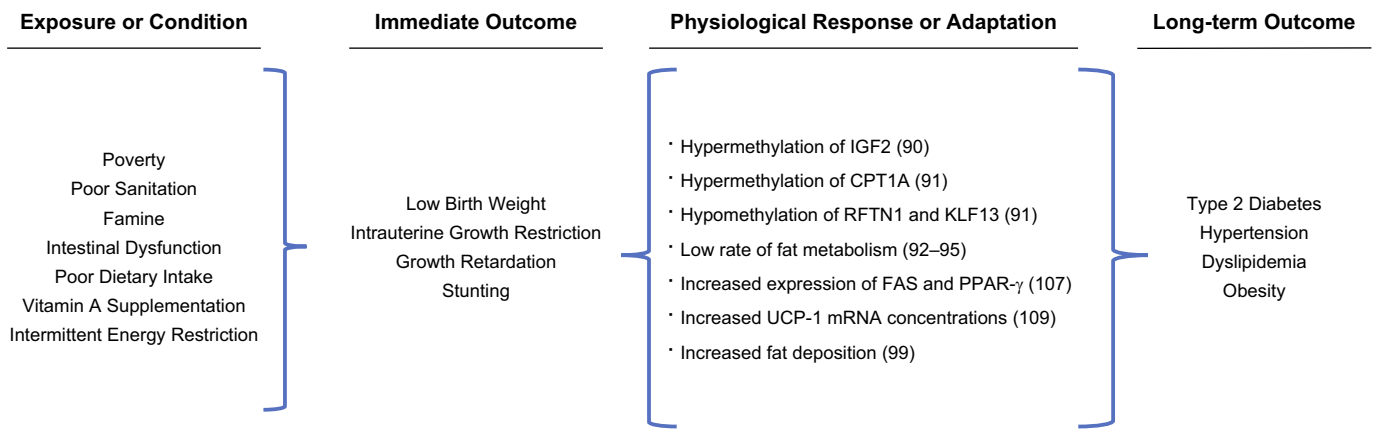

FIGURE 2. Potential social, environmental, or physical exposure that promote poor growth in utero or childhood and associated physiological responses or adaptions (with references) that ultimately contribute to the developmental origins of metabolic diseases. CPT-A, carnitine palmitoyltransferase 1A; RFTN1, Raftlin, lipid raft linker 1; FAS, fatty acid aynthase; KLF13, Kruppel-like factor 13; UCP, uncoupling protein; PPAR, peroxisome proliferator-activated receptor.

influence biological outcomes, there is always the need for corroborating evidence that provides a clear biological mechanism. The literature reviewed below is focused primarily on human and some rodent and nonhuman primate data as shown in **FIGURE 2**, which depicts the relationship between specific exposures and physiological outcomes, but more explicit mechanisms are gleaned in subsequent discussions of basic experimental data below in this review (see ROLE OF THE PLACENTA IN FETAL GROWTH AND METABOLIC DISEASES and ADVERSE IN UTERO ENVIRONMENT AND METABOLIC DISEASE).

1.4.1. Epigenetics and in utero famine exposure.

Recently, with the advent of new techniques to study epigenetic modifications, a number of investigators have retrospectively studied the epigenetics of in utero famine exposure. For adults from the Dutch famine, prenatal malnutrition-associated differentiated methylated regions (P-DMR) were analyzed according to timing of gestational exposure to the famine (91). Differential methylation patterns existed in six P-DMRs that were associated with genes that influence growth and metabolic functions, such as insulin signaling (INSR), pancreatic beta cell functioning (SMAD7), as well as lipid (CPT-1A) and cholesterol (KLF13) metabolism. More important, the methylation patterns identified had positive correlations with the phenotypic outcomes associated with each gene, suggesting that early exposure to nutrient restriction may influence epigenetic control of metabolic processes later in life. Consistent with the results from the Dutch famine, adults who experienced gestational exposure to famine in Bangladesh and were underweight as adults were more likely to be hyperglycemic compared with unexposed adults (8). Moreover, those same men who had been exposed to famine in utero and remained underweight as adults showed differences in methylation patterns, primarily hypomethylation, in 6 of 16 metastable epialleles (ME) compared with men who were exposed to the famine postnatally or were never exposed (8). To further illustrate these results, a study was conducted in the Gambia during seasonal changes in food availability (dry vs. rainy seasons corresponds to nutrient-limited vs. nutrient-rich seasons), where access to total energy and methyl-donor nutrients, such as folate and the B vitamins, is severely restricted (100). Analyses of peripheral blood lymphocytes showed that there was significant hypermethylation of six ME in infants who were conceived during the rainy season compared with those conceived during the dry season. Perhaps more profound is the fact that maternal periconception biomarkers for methyl-donor nutrients significantly predicted methylation patterns of the offspring. Indeed, epigenetic analyses from the Chinese famine study yielded similar results, such that adults who were exposed to the more severe famine in utero had significantly higher total cholesterol and low-density lipoprotein concentrations compared with adults who were never exposed to the famine, independent of age and sex (90). Similar to the epigenetic studies of the Dutch famine, adults exposed to the severe famine had increased methylation of the CpG1 site of the IGF2 gene compared with those exposed to moderate or no famine.

1.4.2. Dysfunctional energy expenditure.

In terms of energy expenditure, an early study of growth and metabolism compared the resting metabolic rate (RMR) between growth-retarded (HAZ less than −1.50) and control children in Guatemala and found no differences in RMR, even when controlling for lean body mass

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(LBM), the most metabolically active tissue (101). A study in Brazil also found no differences in RMR between growth-retarded children and control children, controlling for LBM (102). Yet others have reported a lower rate of energy expenditure in growth-retarded children compared with normal-height children, but these studies compared RMR per unit body weight and did not use linear regression analyses, the accepted statistical method for adjusting for body weight or LBM between groups (103–105). Again, the divergence in results is most likely due to the use of statistical methods that control for the mass of metabolically active tissue; using ratios can often result in statistically significant differences where no actual difference exists. This is apparent when one considers that studies in which metabolic differences were reported used ratios of energy metabolism per unit body weight of LBM rather than multiple linear regression analysis. It is now accepted that multiple linear regression analysis is the more appropriate statistical approach for studying such parameters (106), given that the mathematical use of ratios requires the two variables to have a linear relationship that includes passing through the 0 intercept, which LBM and energy expenditure do not, thus necessitating the use of advanced statistical methods over more simple tests.

1.4.3 Adaptations in substrate metabolism.

Although studies of energy expenditure provide important information about metabolism, more intricate aspects of basal metabolism, specifically the metabolism of macronutrients, can better inform potential mechanisms related to metabolic adaptations following linear growth restriction (**FIGURE 3**). Perhaps the first study of metabolic adaptations and childhood growth retardation was conducted in a cohort of children in Brazil in which growth-retarded children had lower rates of fat oxidation compared with normal-height children from the same shantytowns of São Paulo (92). Similar results have been published from distinct genetic, ethnic, and geographical cohorts including adult men from the Hertfordshire Cohort in the United Kingdom (93), a study of seminomadic adults from the Buryat communities in Siberia who experienced growth retardation after the collapse of the Soviet Union (95), and a study of North Korean children who were either stunted or short for age (94). All three studies consistently found that study participants who were shorter than their peers had a significantly lower rate of fat oxidation. Potential mechanisms to explain these results are considered exploratory, as it is difficult to conduct invasive biological measures of metabolism because of ethical constraints on studying poor growth in vulnerable populations. Nonetheless, it is important to reiterate that outcomes of various studies of body composition or energy metabolism may be attributed to differences in study design, statistical analyses, or the socio-economic environment in which the study was conducted.

There are also a number of studies of nonhuman animals that address the question of metabolic adaptations resulting from energy and/or nutrient restriction during

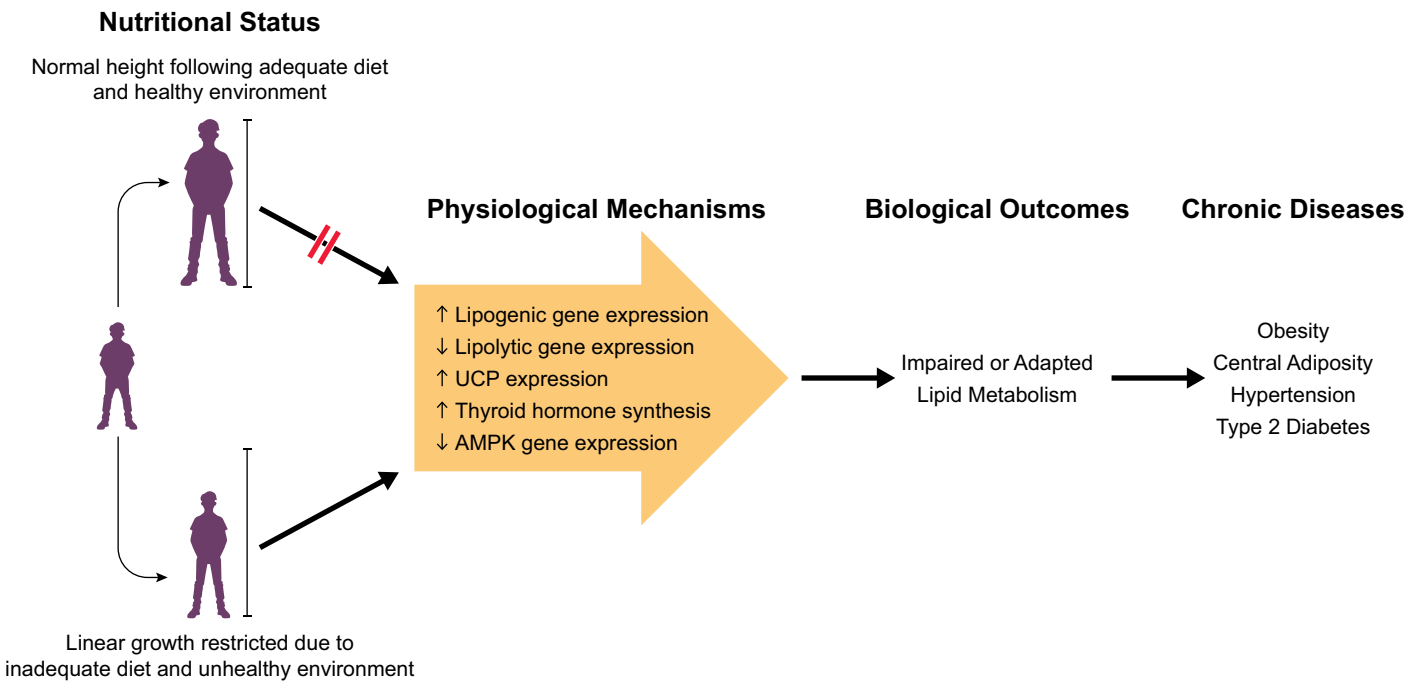

FIGURE 3. Illustration of physiological mechanisms to support association between poor growth in childhood and metabolic adaptations that promote chronic diseases in adulthood. AMPK, AMP-activated protein kinase.

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gestation or early childhood. For example, a study of pigs born with low (L) or normal (N) birth weight received an ad libitum diet after birth and then were fed an energy restriction (R) diet after weaning (96). Not only did the L pigs have significantly lower fat oxidation compared with the N pigs, but the rate of fat oxidation was ~50% lower in the LR pigs compared with the NR pigs. Biochemical explanations for these findings may be found in a study of protein-restricted pigs that were subsequently fed a 14% protein diet and were found to have increased intramuscular fat content as well as increased expression of lipogenic genes (e.g., FAS, PPARγ, and FABP4) compared with pigs fed a 20% protein diet (107). Interestingly, the pigs on the low-protein diet had a lower expression of lipolytic genes compared with pigs fed the control diet. In addition, studies of sheep demonstrated that energy restriction alters substrate metabolism in a tissue-specific manner that favors carbohydrate metabolism (108). Finally, a study in rodents found that vitamin A supplements in early life resulted in a reduced expression of key adipogenic markers (PPARγ and lipoprotein lipase) and increased adiposity when rats were fed a high-fat diet compared with control rats on the same diet (97). More important, the gain in FM was independent of body weight, which is suggestive of adipocyte hyperplasia.

To further illustrate the influence of energy restriction on energy metabolism and body composition, mice exposed to intermittent fasting (IF) three times a week had lower fat metabolism compared with the ad libitum (AL) group, regardless of whether they were fed a high-fat or normal diet (109). The IF mice had lower gonadal and inguinal fat pad weights and increased energy expenditure compared with the AL mice. Furthermore, the IF mice had increased UCP-1 mRNA concentrations in both fat depots, suggesting that fasting stimulated an increase in the uncoupling of energy expenditure in these depots and could explain the increase in total energy expenditure as a response to intermittent energy restriction. This "browning" of white adipose tissue may reflect the modified characteristics of the fat depot, as it resembled brown fat that is more energetic and associated with higher energy expenditure. Yet, given that this adaptation occurred after a period of refeeding, it is difficult to determine whether the changes in UCP-1 mRNA concentrations were a response to energy restriction or refeeding. Nonetheless, a parallel study was conducted in which thyroid hormone metabolism in skeletal muscle was measured in rats that were semistarved and refed to promote "catch-up" fat (110). After refeeding, the refed animals had depressed protein synthesis in skeletal muscles and a lower rate of 3,5,3′-triiodothyronine (T_3) synthesis. It was concluded that severe energy restriction essentially limits energy availability for protein synthesis and drives available nutrients toward fat deposition rather than energy utilization.

It is important to emphasize that specific metabolic adaptations that elicit endocrine or molecular responses to preserve body fatness generally will not be manifested without concomitant "environmental" changes, such as increased exposure to processed or refined foods for humans or refeeding protocols for nonhuman studies. In one such study of pigs, those who were energy restricted and then refed on an ad libitum diet experienced compensatory growth and deposited more fat in the subcutaneous depot than the control group (99). The refed pigs also had differential expression of 86 genes that are associated with key regulatory and signaling pathways associated with homeostasis and energy metabolism. Specifically, the refed pigs appeared to downregulate genes associated with the AMP-activated protein kinase (AMPK) pathway. For example, the control pigs, compared with the refed pigs, presented with an upregulation of genes that regulate carbohydrate metabolism, including genes that promote translocation of glucose transporters and stimulate glycolysis. These molecular adaptations are consistent with the phenotypic findings that refed pigs gained more back fat and had greater intramuscular fat compared with control pigs. Thus, despite differences in species and study protocols, energy or protein restriction during key periods of growth appears to elicit metabolic adaptations similar to what is reported in human studies of growth retardation, shedding light on potential mechanisms that explain why poor growth is associated with metabolic diseases in adulthood.

1.4.4. Summary.

The studies presented thus far have ranged from historical studies of famines to clinical studies of growth-retarded humans to molecular analyses of pig and rodent experiments. A consistent pattern emerges from these studies, simply that energy or nutrient restriction during key periods of growth is followed by specific adaptations in hormonal or biochemical processes that favor fat deposition, especially when paired with postnatal environmental changes, such as exposure to adequate, energy-rich foods. However, it is important to discuss a caveat to interpreting these studies en masse, as the scientific philosopher Karl Popper noted that regardless of the number of positive observations made, one cannot ignore the potential that a negative outcome may be found in the future (111). In that vein, it is important and necessary to acknowledge that many of the studies presented come from a range of animal species that may have acutely different physiological systems that could respond to various perturbations in subtly different manners. Likewise, studying health outcomes of older humans following a nutritional insult many decades earlier may not be able to

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account for any of the multitude of environmental factors (e.g., exercise, smoking, exposure to environmental toxins, stress) to which laboratory animals are not exposed. Finally, the science of life course analysis is becoming more prominent in the human biology arena, and it is important to recognize that the timing of various insults, either in utero or during infancy or childhood, relative to measures of metabolism or disease development may contribute to disparate results among studies. Thus, these limitations are not trivial; nor are they insurmountable, provided a proper perspective is taken when comparing a large cross section of research.

Nonetheless, the results presented thus far do lend credence to the hypothesis that poor growth results in a number of physiological adaptations that may promote chronic diseases under favorable environmental conditions. This is consistently observed in clinical and animal models of fetal growth restriction whereby the enriched postnatal environment adversely affects the function of the liver, adipose, pancreas, and heart. However, before these postnatal outcomes manifest, the adverse in utero environment is first sensed and unfortunately impacted by the placenta. ROLE OF THE PLACENTA IN FETAL GROWTH AND METABOLIC DISEASES provides strong evidence that the maternal-fetal interface recognizes and attempts to adapt to the maternal insult but, however, ultimately contributes to the impaired fetal development that results. The role of the placenta in normal and abnormal fetal growth is reviewed, including oxygen and nutrient transport along with endocrine function.

2. ROLE OF THE PLACENTA IN FETAL GROWTH AND METABOLIC DISEASES

As noted above, Barker and others first established the importance of adequate intrauterine growth for lifelong health (3). Indeed, numerous epidemiological studies across the globe have since described the adverse conditions confronting human populations that contribute to poor growth in utero and during early childhood (52, 64, 73, 112). The role of the placenta in determining the fetal growth trajectory is supported by human studies of poor placental functional capacity associated with growth failure in utero as well as activation of placental nutrient delivery in cases where fetal overgrowth is observed. In this section, we present evidence for a critical role of the placenta to both respond to maternal conditions and modulate fetal growth by changing the delivery of nutrients needed to sustain growth. These short-term adaptations might be beneficial short term for fetal survival but ultimately can contribute to poor neonatal outcomes and an increased risk of noncommunicable diseases later in life.

2.1. Placental Function and Fetal Growth

In humans, as in all eutherian mammals, pregnancy results from internal fertilization and development of the embryo and fetus. Carefully orchestrated changes in maternal physiology and a well-functioning placenta are required to provide gas exchange, supply macro- and micronutrients, and remove waste products. In addition, the placenta is a versatile endocrine organ secreting hormones that promote the maternal metabolic and cardiovascular adaptations to pregnancy, including the development of maternal insulin resistance and the increase in uteroplacental blood flow across gestation. Given the broad discussion above of epidemiological and clinical studies of maternal diet or body composition and birth outcomes, it is important to present potential mechanisms that may reside in placental development and physiology that may impart disease risk for infants born intrauterine growth restricted (IUGR, birth weights in the lowest 3–5% centiles of a reference).

It is clear that alterations in placental development and/or function adversely impact fetal development that results in the birth of an infant classified as SGA or IUGR. However, at the opposite end of the spectrum is fetal overgrowth, resulting in the delivery of a baby classified as large for gestational age (LGA, birth weight above the 90% percentile) or macrosomia when a baby is born weighing >4,000 g at any gestational age. As discussed above, being born small or large relative to a healthy standard increases the risk of developing obesity and other metabolic disorders (63, 64, 67, 68, 101, 113). As changes in placental function are believed to directly contribute to abnormal fetal growth and body composition, the placenta plays a critical role in the developmental programming of metabolic disease (114). Thus, a better understanding of molecular mechanisms regulating placental function, including maternal and fetal signals (115), may inform us on the underpinnings of the intrauterine origins of metabolic disease and lead to the development of novel intervention strategies.

2.1.1. Placental development and function.

The placenta originates from the earliest cellular differentiation in the embryonic blastocyst and comprises several trophoblast cell lineages. The inner cell mass develops into the fetus, and the extraembryonic cells differentiate into the trophectoderm that becomes the mature placenta and fetal membranes (116). Robust development of the fetal (umbilical) and maternal (uteroplacental) vascular beds is critical for optimal delivery of nutrients and gas exchange. Ultimately, human placental development brings these two circulations into close approximation, separated by only two cell layers, a transporting

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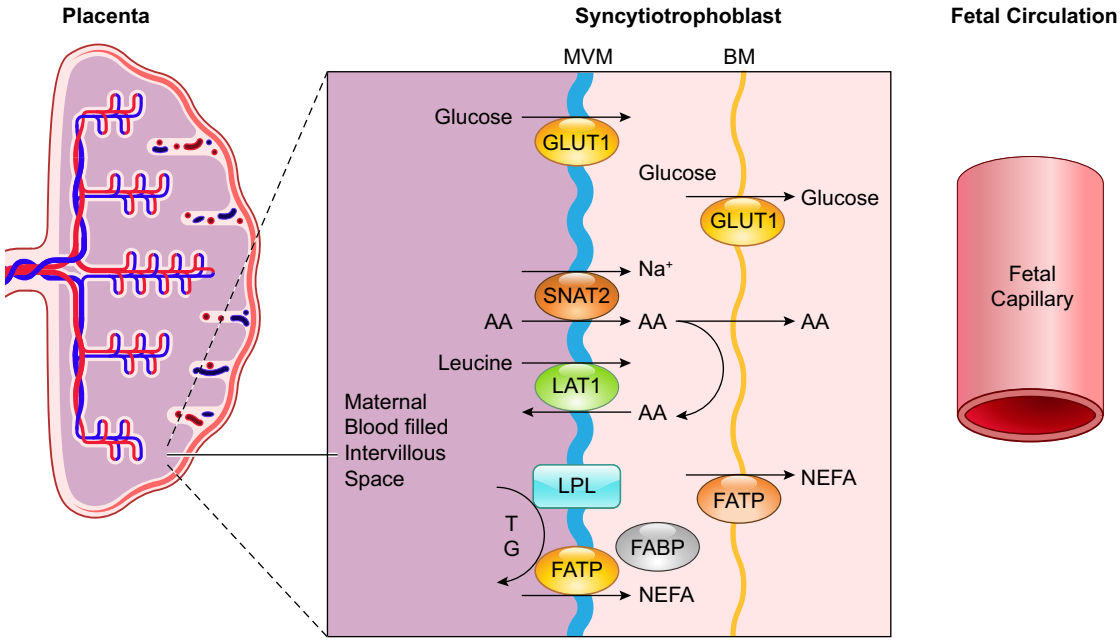

FIGURE 4. Placental anatomy and transporter localization in the syncytiotrophoblast: amino acid (AA) transport across the syncytiotrophoblast (ST) to the fetal capillary endothelial cell; glucose transport; and lipid transport. BM, basal plasma membrane; FATP, fatty acid transporting protein; GLUT, glucose transporter; MVM, microvillous plasma membrane; SNAT2, sodium-dependent amino acid transporter isoform 2; LAT1, leucine transporter isoform 1; TG, triglyceride; LPL, lipoprotein lipase; FABP, fatty acid binding protein; NEFA, non-esterified fatty acid.

epithelium called the syncytiotrophoblast and the fetal capillary endothelium. The syncytiotrophoblast, illustrated in **FIGURE 4**, is a polarized syncytial epithelium that serves as both the primary barrier and the key transporting cell between maternal and fetal blood supplies. Importantly, the composition of nutrients in fetal blood is distinct from the mother throughout gestation; therefore, the placenta does not simply function as a semipermeable filter. Mechanisms for solute transfer across the placenta include passive and facilitated diffusion, active transport, and endocytosis. Macronutrient transport across this barrier is accomplished through specialized transporting proteins, channels, or exchangers in the plasma membranes of the syncytiotrophoblast (117, 118). Placental transport function is modulated in response to the ability of the mother to provide nutrients as well as in response to fetal demand signals (119). Thus, placental capacity for delivering nutrients changes in response to maternal signaling and directly impacts the fetal growth trajectory, making it a primary cause for pathological fetal growth (120).

2.1.2. Placental blood flow in normal, IUGR, and LGA pregnancies.

Optimal fetal growth is dependent on adequate blood flow on both sides of the placental barrier and is facilitated by placental gas exchange to allow for transfer of oxygen to the fetus and removal of carbon dioxide from the fetal compartment (121, 122). Maternal blood flow to the placenta increases when uterine immune cells and extravillous trophoblast cells transform the spiral arteries in the uterine endometrium and radial arteries in the myometrium, converting tightly coiled vessels to large, unresponsive conduits that open into the placental intervillous space (123). This transformation decreases the resistance in the uteroplacental circulation starting at ~20 wk of gestation (124) and allows for 25–30% of maternal cardiac output to perfuse the placenta by late pregnancy (125). The redirection of maternal blood to the placental circulation is supported by an expansion of the maternal blood volume beginning in early pregnancy (126). Failure to remodel maternal vessels results in ischemia, oxidative stress, low nitrous oxide production, and release of antiangiogenic soluble factors such as fms-like tyrosine kinase 1 (sFLT-1) and Endoglin (sENG) (127). Proangiogenic factors like placental growth hormone (pGH) and vascular endothelial growth factor A (VEGFA) are antagonized by these factors (128), leading to reduced invasion of the trophoblast and maternal endothelial dysfunction. The net effect is a failure of uteroplacental blood flow to increase, which is believed to underlie pregnancy complications such as preeclampsia and IUGR (129, 130).

Increasing uteroplacental blood flow across gestation is paralleled by increased feto-placental blood flow, regulated by vascular tone and angiogenesis (130). Poor placental angiogenesis has been observed

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in IUGR pregnancies, but the mechanisms regulating this process are complex and not completely understood. Placental vasculature lacks innervation and autonomic control, making humoral factors of key importance in determining blood flow (131). In fact, impaired fetal vascular development has been linked to alterations in prostaglandin E_2 reactivity (132) and endothelin-1 levels (133) and an imbalance in branching and nonbranching angiogenesis resulting in longer unbranched capillary loops in the villous vascular tree (134). A number of angiogenic (VEGFA, pGH, fibroblast growth factor, angiopoietins 1 and 2), as well as antiangiogenic (sENG, sFLT-1) factors have been implicated in feto-placental vascular development. Data on the role of these factors are not consistent between various animal models of IUGR or in human IUGR (135). Doppler ultrasound measures of reduced umbilical artery blood flow are indicative of poor feto-placental perfusion and restricted fetal growth, but these measures lack adequate specificity to be used clinically to predict long-term outcomes (124, 136). Recently, a large clinical study combined Doppler ultrasound measures with known biomarkers for angiogenesis, inflammation, and pregnancy disorders but did not find significant improvement in prediction of poor intrauterine growth (137). Inadequate angiogenesis in the placenta has also been suggested to reflect poor vascular development in fetal organs such as lung, heart, and pancreas (138–140). Therefore, markers of poor placental angiogenesis may provide predictive biomarkers for postnatal complications such as bronchopulmonary dysplasia and cardiovascular and metabolic disease due to poorly developed blood supply in these critical organs (141–144).

2.1.3. Placental nutrient transfer in normal, IUGR, and LGA pregnancies.

In terms of fetal nutrition and growth, the placenta plays a critical role in the transfer of nutrients, such as glucose and key micronutrients, to promote and sustain fetal growth and development. Energy required for fetal growth comes from glucose, the primary substrate for fetal energy metabolism, which is transferred across the placental barrier by facilitated diffusion (118), and fetal glucose levels remain lower than those of the mother and fluctuate with maternal glycemic status. Glucose transporters are embedded in the plasma membranes of the syncytiotrophoblast and facilitate the movement of glucose down its concentration gradient (145). Several non-insulin-dependent glucose transporters (GLUTs) are expressed in the human placenta, including GLUT isoforms 1, 3, 9, and 12 (146). The apical or microvillous plasma membrane (MVM) of the syncytiotrophoblast has highly abundant GLUT1 transporter expression, allowing for rapid uptake of glucose from maternal blood in the intravillous space (145). The placenta metabolizes ~30% of the glucose taken up from the uteroplacental circulation (147), and glucose transporters in the fetal-facing basal plasma membrane (BM) allow glucose to flow down its concentration gradient to the fetal capillary. The BM is believed to be the rate-limiting step for glucose transfer because of the lower expression of GLUT proteins and much smaller surface area compared with the MVM (145), suggesting that any alterations in the BM may result in poor fetal growth.

In IUGR, inadequate placental glucose transfer due to a reduced placental surface area may contribute to slow growth rates, but no significant changes in GLUT1 expression in MVM or BM have been reported in these pregnancies (145, 148). In pregnancies complicated by obesity, where fetal growth is more likely to be accelerated, expression of GLUT1 in BM is correlated with birth weight (149), and several GLUT isoforms (1, 4, and 9) were recently reported to be positively correlated with fetal growth in pregnancies complicated by gestational diabetes (GDM) (150). It was recently reported that insulin-responsive GLUT4 is found in the human placental BM and that changes in expression occur with activation of the insulin receptor on the MVM. These data suggest control of glucose delivery through high postprandial maternal insulin to increase delivery when glucose is abundant (151). Once in the fetal circulation, glucose stimulates the fetal pancreas to release insulin, a strong promoter of fetal growth (152). In pregnancies complicated by maternal hyperglycemia such as those of obese and diabetic mothers, increased placental flux of glucose to the fetus likely contributes to accelerated fetal growth (153).

With regard to micronutrients, the impact of maternal diet on offspring body composition is discussed above in this review and is most likely dependent on placental delivery of micronutrients. For example, adequate Ca^{2+} is essential for fetal bone mineralization, and adequate fetal Ca^{2+} is ensured when Ca^{2+} levels are higher than those of the mother, facilitated by Ca^{2+}-ATPase localized in the BM to transport Ca^{2+} against its gradient (154). The importance of this process is demonstrated by the observation that growth-restricted fetuses have relatively "normal" bone length and density compared with other compartments of body composition (154). Ca^{2+}-ATPase expression and activity are higher in the BM of IUGR placentas, suggesting a compensatory mechanism to support bone development in the fetuses who are slowing somatic growth of lean mass and FM (155). This mechanism is particularly relevant to stunting in early childhood as well, since placental Ca^{2+} transfer may influence linear growth in utero, and would be of critical interest to better understand the life course effects of placental physiology.

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Fetal growth requires rapid and sustained protein synthesis; thus lean tissue accretion during fetal growth requires adequate protein synthesis and amino acids are higher in fetal circulation compared with the mother because of two key secondary active transport systems in the syncytiotrophoblast that are dependent on the cellular Na^+ gradient generated by Na^+-K^+-ATPase. System A is an amino acid transporter in the MVM responsible for uptake of nonessential amino acids against their concentration gradient energized by the inwardly directed Na^+ gradient (156). This uptake creates high intracellular concentrations of amino acids, which then diffuse across the BM, mediated by efflux transporters and exchangers, to enter the fetal blood (157). System L exchanges the high intracellular levels of nonessential amino acids for essential amino acids, such as leucine, in the maternal circulation (158). Such coordinated transporter functions allow for a net accumulation of both essential and nonessential amino acids in the fetal compartment to support protein synthesis and growth. In fact, reduced placental amino acid transport capacity is a consistent feature of IUGR pregnancies (159–167). Conversely, increased amino acid transport capacity has been reported in placentas from pregnancies with LGA babies of both obese and diabetic mothers, but this has not been consistently reported in all studies (117, 150, 168–176).

Lipids are essential for neural development and hormone synthesis, and maternal circulating lipids increase across gestation to provide fatty acids (177) that serve as an energy source as well as structural building blocks for the fetus and are precursors for important signaling lipids (178). However, the mechanisms for lipid transfer across the placental barrier are not fully understood. Lipoprotein receptors in the MVM allow complex maternal lipids to bind to the syncytiotrophoblast (179), where lipases on the MVM surface release nonesterified fatty acids to be taken up by the placenta (180). Fatty acid transporting proteins (FATPs) and CD36 fatty acid translocase are localized to both plasma membranes in placenta (181). Lipase activity was found to be lower in pregnancies complicated by IUGR and higher in diabetic pregnancies delivering LGA infants (182). Moreover, in pregnancies complicated by IUGR, an upregulation of fatty acid transporters was found in the MVM (183), suggesting a compensatory mechanism for delivering much-needed lipids to the slow-growing fetus. A novel lipid transporter for phospholipids, Major Facilitator Superfamily Domain (MFSD2a), was recenly reported to be present in the human placenta. Expression of MFSD2a, a transporter with a strong affinity for lysophosphatidylcholine species that contain docosahexaenoic acid (DHA), correlated with the percentage of DHA in the umbilical circulation of women with GDM (184). A strong association between MFSD2a expression and umbilical cord lysophosphatidylcholine-DHA suggests a role for this transporter in supplying n–3 long-chain polyunsaturated fatty acids to the fetus (185).

2.1.4. Placental hormones in normal, IUGR, and LGA pregnancies.

Endocrine regulation of fetal growth is tightly regulated by the placenta, as the syncytiotrophoblast secretes hormones that coordinate maternal adaptations to pregnancy that support the growth of the developing fetus and prepare the mother for lactation. Changes in placental endocrine functions may contribute to adverse fetal development and contribute to the programming of metabolic disorders in the offspring, yet underlying mechanisms are not completely understood. Examples of key hormones secreted by the placenta that have distinct roles in normal and impaired maternal-fetal physiology are listed in **TABLE 1**, and their roles in normal and abnormal fetal development along with potential links to postnatal metabolic disease are discussed below.

Specifically, human chorionic gonadotropin (hCG) is produced primarily by syncytiotrophoblasts and has a structure similar to luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Key hCG functions include autocrine/paracrine stimulation of placental growth and differentiation, maintaining progesterone production by the corpus luteum until the placenta takes over as the main site for progesterone synthesis, proangiogenic effects in the uterine and placental vasculature, promotion of trophoblast invasion, and suppression of the maternal immune system to prevent rejection of the conceptus (189, 190). In early pregnancy, hCG does not predict the development of pregnancy complications with the sensitivity required for a clinically useful biomarker (191). This may, in part, be due to imprecise conception dating and rapid changes in hCG levels in early pregnancy and partly explains why hCG has not been found to predict developmental programming of metabolic disease.

Likewise, human placental lactogen (hPL), or human chorionic somatomammotropin, is produced mainly by the syncytiotrophoblast and is structurally very similar to growth hormone (GH). Increases in circulating hPL reflect changes in placental mass (189, 192). hPL binds to GH and prolactin receptors and modulates maternal lipid and carbohydrate metabolism during pregnancy. Specifically, hPL activates maternal adipose tissue lipolysis, contributing to a pronounced increase in maternal circulating lipids during pregnancy (189). Moreover, hPL increases maternal pancreatic mass and insulin secretion, contributing to maternal postprandial hyperinsulinemia to compensate for insulin resistance in pregnancy

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Table 1. ***Placental hormone functions, changes with pregnancy pathology and associations with DOHaD***

Hormone	Function	IUGR*	Obesity/Diabetes*	DOHaD	References
Human chorionic gonadotropin (hCG)	• Stimulates trophoblast invasion and growth • Proangiogenic • Immunosuppression			Indirect associations	67, 186
Placental lactogen (hPL)	• Increases maternal lipolysis and glycolysis • Stimulates maternal pancreatic β cell expansion	Decreased	Increased	Indirect associations	163
Placental growth hormone (pGH)	• Decreases maternal insulin sensitivity • Stimulates IGF release • Promotes growth	Decreased	Increased	Hypertension Insulin resistance	187
Insulin-like growth factor (IGF)	• Stimulates placental nutrient transport and hormone release	Decreased	Lower IGFBP	Hypertension Insulin resistance	85, 188
Progesterone	• Enhances implantation • Uterine quiescence	Increased	Decreased	Indirect associations	187
Estrogen	• Stimulates blood flow • Angiogenesis • Increased nutrient delivery	Decreased	Increased	Insulin resistance	183
Leptin	• Decreased apoptosis • Increased invasion • Immunosuppression	Decreased	Increased	Appetite regulation Hypertension	67

IGFBP, IGF binding protein; IUGR, intrauterine growth restriction. *Relative changes in hormone levels are in comparison to healthy pregnancies with appropriate growth for gestational age fetus.

and maintain euglycemia (193). hPL is also secreted into the fetal circulation but, however, at much lower concentrations than in the maternal circulation, where it has been proposed to stimulate the growth of several tissues (194, 195). Placental hPL production is therefore highly relevant to fetal growth because of the metabolic impact on the mother and growth stimulation in the fetus, but few studies clearly link hPL directly to pathological fetal growth or long-term health risk in the offspring (196).

In addition, human placental growth hormone (pGH) is structurally highly related to hPL and prolactin and supports fetal growth by promoting maternal gluconeogenesis and lipolysis (192) to increase maternal circulating nutrients for placental uptake and transfer to the fetus (197). This variant of pituitary growth hormone, which is normally secreted in a pulsatile manner, is produced constitutively by the syncytiotrophoblast from 15–20 wk of gestation through parturition, replacing maternal pituitary growth hormone for the second half of gestation (192, 198). The physiological roles of pGH are similar to pituitary growth hormone, such as stimulating insulin-like growth factor 1 (IGF-1) and modulating maternal metabolism, including insulin resistance (189). Reports of association between pGH levels and pregnancy complications are varied, but reduced fetal growth has been associated with low maternal pGH levels (196, 199) and LGA infants of obese and GDM mothers are associated with increased pGH in the maternal circulation (200, 201). Notably, pGH expression has been linked with adult height, suggesting that intrauterine growth as well as adult longitudinal growth are determined by placental hormones and intrauterine exposure (202). This provides a strong link between placental hormone synthesis and offspring growth restriction or stunting when the mother has poor access to nutrition during pregnancy.

At the same time, insulin-like growth factors (IGFs) are critically important for growth and differentiation during development. IGF-1 promotes maternal tissue growth, trophoblast invasion, and placental blood flow as well as linear growth in the postnatal period (203). IGF-1 is regulated by pGH during pregnancy (204), which in turn is highly responsive to maternal nutrient status. IGF-2 levels are higher than IGF-1 in both maternal and fetal circulations (205). Nutrient transporter activity and expression as well as placental hormone production are regulated by IGF-2 (206). These signaling interactions create a strong link between maternal nutritional status,

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pGH/IGF, and fetal growth, as evidenced by placental IGF-2 expression being positively correlated with birth weight (207). Bioactivity of IGF is also regulated by multiple IGF binding proteins (IGFBPs). In fetal life, IGFBP-1 represents the most important binding protein, and the affinity of IGFBP-1 to bind IGF-1 is modulated by phosphorylation, enhancing the affinity for IGF-1 binding (42), providing an additional level of control in this critical growth-regulating network. IUGR is associated with lower IGF-1 and -2 in the umbilical cord (208) and hyperphosphorylation of IGFBP-1 in both the fetal (43) and the maternal (209) circulations. On the other hand, GDM is associated with lower levels of IGFBP-1 and -7, which likely results in increased IGF bioactivity in these pregnancies (210).

Finally, placental estrogens are also key steroids that influence fetal development and impact postnatal metabolic disease. Estrogens are produced in the syncytiotrophoblast, and the predominant precursor, DHEA-S, is synthesized by the fetal adrenal cortex and delivered to the placenta, where it is converted to estrogen by CYP19A1 (aromatase) and released preferentially to the mother (211). Functions of estrogen in pregnancy are diverse, including stimulation of uteroplacental blood flow, endometrial growth, placental angiogenesis, and nutrient uptake (211). Placental estrogens act on the maternal liver to increase very low-density lipoprotein (VLDL) production, supporting the increase in circulating triglycerides in the second half of pregnancy (189). Moreover, both high and low intrauterine estrogen exposure have been associated with adult insulin resistance (212, 213).

2.1.5. Placental exosomes in normal, IUGR, and LGA pregnancies.

Fetal growth is also regulated by placental signaling other than the endocrine systems discussed above. In particular, increased circulating extracellular vesicles (EVs) with surface trophoblast markers suggest that the placenta is communicating with the mother through EV signaling (214). The vesicle cargo is diverse, including proteins, lipids, and nucleic acids, which can be taken up by target cells in the maternal vasculature or immune cells to modulate maternal physiology and facilitate adaptation to pregnancy (215). One role of placental EVs is thought to be immune tolerance to prevent fetal rejection (216), but other functions, such as spiral artery remodeling, trophoblast invasion, and modulating cytokine release, have also been attributed to EVs and a subgroup of placental EVs called exosomes. Exosomes from the placenta have been proposed to play a role in pregnancy complications, including GDM and preeclampsia (215, 217), through modulation of specific exosome content that has been shown to be affected by the local placenta microenvironment (216). The ability to modulate exosome content allows the placenta to send divergent signals to the mother in pregnancies complicated by low uteroplacental blood flow or maternal metabolic disease or in conditions of increased oxidative stress (215). A specific role for exosomes to modify metabolic processes in the mother across gestation has been proposed, but additional cause-and-effect experiments are needed. Nonetheless, whether placental EVs are released to the fetal circulation to modulate organ development or as a programming mechanism is less clear and remains an area of active research (218).

2.2. The Placenta as a Nutrient Sensor and Fetal Development

A major role of the placenta involves regulating blood flow, nutrient transport, and endocrine signaling for proper fetal development, and more recently the placenta has been suggested to function as a nutrient sensor (119) and is regulated in response to an array of maternal signals that aid in determining nutrient transfer to the developing fetus. Moreover, the association between the activity of placental nutrient transporters and fetal growth, birth weight, and adiposity suggests a mechanistic link between placental nutrient transport capacity, fetal growth rates, and maternal body composition (114). A better understanding of how placental transport functions are regulated may provide novel therapeutic avenues to prevent or alleviate abnormal fetal growth and therefore long-term fetal programming of metabolic disease. For example, if maternal nutrient status or uteroplacental blood flow is low, this is "sensed" by the syncytiotrophoblast, which responds by slowing its own growth and downregulating the expression and/or activity of nutrient transporters, thereby slowing fetal growth. By adjusting fetal nutrient delivery to match the ability of the mother to provide substrates for growth, the placenta functions as the arbiter of intrauterine growth. This premise is further supported by higher IGF-1 levels, mechanistic target of rapamycin (mTOR) activation, and increased amino acid and fatty acid transporter expression in placentas of GDM and obese mothers (172, 176, 181, 219), in whom fetal overgrowth is more common. Conversely, IUGR pregnancies are known to be associated with lower levels of growth factors, smaller placentas, and reduced mTOR and amino acid transport capacity including in animal models of protein or calorie restriction during gestation that mimic poor maternal nutrition or famine (220–223). Given the complex nature of how the placenta regulates nutrient delivery to the fetus, a thorough discussion of potential pathways is necessary.

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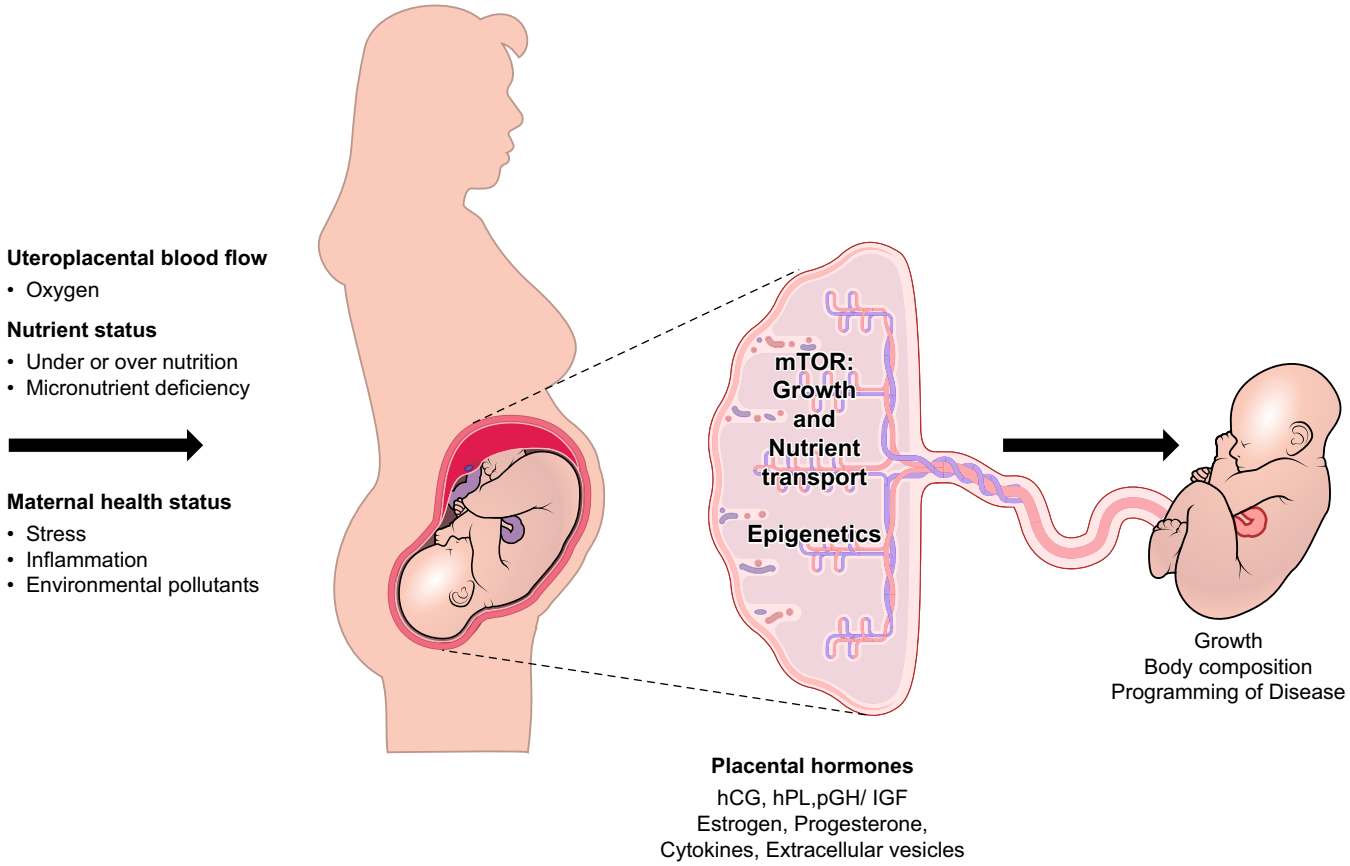

FIGURE 5. Placental mechanistic target of rapamycin (mTOR) is responsive to a wide variety of upstream inputs including macronutrient availability, oxygen, energy status, and hormonal growth signals and in turn regulates placental growth and nutrient transporter function, which leads to changes in fetal growth rate, body composition, and developmental programming. hCG, human chorionic gonadotropin; hPL, human placental lactogen; IGF, insulin-like growth factor; pGH, placental growth hormone.

The mTOR signaling pathway responds to multiple metabolic signals and regulates key placental functions. This signaling pathway has been proposed as a central component of a placental nutrient sensor (224). Specifically, as shown in **FIGURE 5**, mTOR regulates placental growth and nutrient transporters and is responsive to a wide variety of upstream inputs including macronutrient availability, oxygen, energy status, and hormonal growth signals (225). In the human placenta, these signals originate predominantly in the mother and inform the syncytiotrophoblast about her nutritional and health status. There are two mTOR complexes (mTORC1 and mTORC2) that respond to nutrient signals by modulating downstream kinase activities, which in turn control fundamental cellular processes such as protein synthesis, cytoskeleton activity, and proliferation (226). In fact, reducing mTORC1 or mTORC2 by siRNA silencing in cultured primary human trophoblast (PHT) cells resulted in a significant reduction (−50%) in amino acid transport activity due to loss of amino acid transporter localization in the MVM (227). Conversely, siRNA targeting to reduce deptor expression in PHTs, the endogenous mTOR inhibitor, caused a dramatic increase in both expression and activity of amino acid transporters (228).

Emerging evidence also suggests a strong link between placental mTOR signaling, cellular lipid metabolism, and amino acid transporter activity. In cultured PHT cells, incubation with different fatty acid species differentially modulates mTOR activity and amino acid uptake. Treating PHT cells with oleic acid (OA) activated mTOR and stimulated amino acid uptake through System A (229). Conversely, treatment with docosahexaenoic acid (DHA) inhibited mTOR and lowered System A activity (230), suggesting that pregnancies associated with maternal hyperlipidemia (e.g., obesity and GDM), which have higher levels of OA in circulation, may be contributing to activation of placental mTOR, resulting in greater amino acid delivery, and potentially contribute to the development of LGA infants more commonly found in these mothers (231). Likewise, the increasing lipid levels in the maternal circulation across gestation, especially species like OA, would stimulate nutrient delivery to the fetus by coordinating fatty acid and amino acid transport, likely contributing to the higher birth weights in these pregnancies.

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Interestingly, women with adequate DHA in their diet may provide a necessary counterbalance to the stimulation by OA, confirming studies that a well-balanced diet with foods containing ω–3 long-chain polyunsaturated fatty acids is more likely to result in healthy birth weight because of the interactions of nutrient levels and placental function.

Extending this discussion of maternal diet and fetal growth, it is well documented that low maternal folate status is associated with reduced fetal growth and birth defects (232, 233), and a potential mechanism for these associations is attributed to placental mTOR, as it is responsive to folate availability and functions as a folate sensor (234). Placental mTOR activity may be regulated by maternal dietary folate levels such that folate deficiency inhibits mTOR signaling and System A amino acid transporter activity in PHT cells (235). System A activity was rapidly restored when folate was returned to normal levels in folate-deprived cultured human trophoblast cells (83). AMP-activated protein kinase (AMPK) is highly responsive to cellular energy levels and is a primary mTOR regulator in trophoblast cells (234). Oxidative phosphorylation in mitochondria is an important contributor to cellular energy production, and mTOR has recently been found to regulate mitochondrial biogenesis in the human placenta (236). Oxygen levels also impact mTOR, as seen in decreased placental mTOR with hypoxia-induced growth restriction in rats (237). Likewise, endoplasmic reticulum (ER) stress and autophagy are regulated by mTOR in human placenta and likely contribute to slow placental growth when oxygen or glucose is limiting (237–239).

Although a variety of stimuli activate placental mTOR, the most-studied hormonal effectors in trophoblasts are insulin and IGF-2, which represent positive maternal nutritional signals that activate mTOR and increase nutrient transport to the fetus (197). Amino acid transport is modulated by changing the expression of transporters in the plasma membrane through ubiquitination by the NEDD4-2 ligase that removes the transporter from the membrane and targets it for lysosomal degradation (228). Indeed, placentas of human IUGR pregnancies have lower insulin and IGF-2, reduced mTOR activation, high NEDD4-2 expression, and lower expression and activity of both System A and System L transporters in the MVM (160). A lower transport capacity for amino acids and reduced mTOR activity have also been described in a wide variety of animal models, including IUGR due to decreased uteroplacental blood flow, hyperthermia, or dietary deficiencies (221, 240, 241). On the other hand, accelerated fetal growth due to maternal obesity is characterized by higher insulin and IGF-2, increased placental mTOR activation, and greater nutrient-transporting capacity (228, 242–244). This relationship is particularly evident in women delivering LGA newborns (176, 245). Indeed, coordination between the mother, placenta, and fetus to modulate nutrient allocation confers an evolutionary advantage by reducing fetal nutrient transfer and preserving the mother's health in low-nutrient conditions. However, when nutrients are abundant and blood flow is optimal, the placental mTOR regulatory system has the capacity to increase placental growth, activate nutrient transporters, and accelerate fetal growth. Producing the largest baby the mother can support in this particular pregnancy provides a strong survival advantage, as larger babies have lower infant mortality and morbidity, but the trade-off for accelerated intrauterine growth includes a number of long-term negative health risks (246). In short, these studies provide potential mechanisms for clinical studies describing how maternal diet and body composition influence infant weight and childhood obesity.

In summary, a direct role for placental mTOR signaling in the homeostatic control of fetal growth has recently been proposed (247). In a proof-of-principle experiment, cultured fetal hepatocytes were incubated with conditioned media from trophoblast cells that were deficient in mTOR signaling, and the hepatocytes responded by increasing phosphorylation and secretion of IGFBP-1. Increased IGFBP-1 with greater affinity to bind IGF will result in a decreased bioavailability of IGF and lead to reduced growth of the fetus (247). This novel concept that placental mTOR not only regulates placental growth and function but also communicates directly with the fetal liver to modulate important growth-regulating signals in the fetus is, as of yet, unproven. However, these preliminary reports support the concept that placental mTOR signaling may be an interesting target for efforts to normalize fetal growth in complicated pregnancies and thereby modify the risk for programming of postnatal metabolic disease.

2.3. Endocrine Regulation of Placental Function

The relationships between maternal metabolic hormones, placental growth phenotypes, mTOR activation, and nutrient transport changes have been consistently demonstrated in human pregnancies and in a wide variety of animal models of pathological fetal growth including rodents, sheep, and nonhuman primates (**TABLE 2**). The premise that placental function is regulated in response to maternal nutrient status is supported by findings that maternal metabolic hormones modulate placental function. In understanding how hormones mediate interactions at the maternal-fetal interface, they themselves could serve as early biomarkers of fetal growth restriction and postnatal metabolic dysfunction. This is best exemplified by insulin signaling in the

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Table 2. ***Changes in maternal insulin, placental mTOR, and amino acid transport in human and animal models of pregnancy pathologies for restricted and accelerated fetal growth***

Pregnancy Condition	Maternal Insulin/IGF*	Placental mTOR Activity*	Placental Amino Acid Transport*	References
Human IUGR	Low	Decreased	Decreased	232, 248
Low-protein diet in rat with IUGR	Low	Decreased	Decreased	249
Nutrient restriction in baboon with IUGR	Low	Decreased	Decreased	221
Human GDM with fetal overgrowth	High	Increased	Increased	172, 246
Human obesity (with fetal overgrowth)	High	Increased	Increased	219
High-fat diet mouse with fetal overgrowth	High	Increased	Increased	242

GDM, gestational diabetes; IUGR, intrauterine growth restriction; mTOR, mechanistic target of rapamycin. *Relative changes in each parameter are compared to healthy pregnancy with normal fetal growth trajectory.

placenta, where activation of the insulin receptor in the placenta promotes proliferation mediated by the activation of two distinct signaling pathways: ERK signaling and activation of mTOR through AKT signaling (250). Insulin and IGF stimulation of mTOR has been demonstrated by phosphorylation of well-established mTOR targets, including S6K/RS6 and 4EBP1, in cultured PHTs (227). High maternal insulin and/or IGF, observed in pregnancies complicated by obesity and/or GDM, are more likely to result in larger placentas and greater nutrient transport expression (251, 252). Conversely, pregnancies complicated by IUGR are characterized by lower maternal circulating insulin/IGF, smaller placentas, and reduced placental amino acid transport capacity (117).

Furthermore, placental hormones, such as pGH and hPL, also contribute to the placental adaptive responses to changes in maternal nutritional and metabolic status. Mothers who fail to gain adequate weight in pregnancy have lower pGH levels, reduced IGF-1, smaller placentas, and low birth weight (253). Reduced pGH secretion prevents further depletion of maternal nutrient reserves and preserves resources to support lactation capacity. Conversely, high levels of hPL in pregnancies exhibiting fetal overgrowth contribute to further expand maternal beta cell mass and insulin production, which maintain maternal fasting normoglycemia despite peripheral insulin resistance and promote nutrient allocation for fetal growth (199).

Glucocorticoids are critically important during development to provide a necessary stimulus for maturation of tissues at the expense of growth (254) and have specific roles in regulating placental function (255) including reduced glucose and amino acid transport (255) and reduced placental lactogen release (256). Increased maternal glucocorticoids occur with maternal stress or poor maternal nutrition and result in decreased placental size in all species studied (257). High maternal glucocorticoids result in a decreased expression and/or activity of several nutrient transporters including GLUT and System A (258, 259). A reduced surface area for transfer and decreased transporter activity will limit nutrient transfer and slow fetal growth in pregnancies with high glucocorticoid levels (260). Placental blood flow may also be negatively impacted by stress, as glucocorticoids reduce *vegf* gene expression and reduce placental vessel size (261). Finally, sexual dimorphism has been reported in the placental response to glucocorticoids, with males being more sensitive and having greater inflammatory and vascular responses (262), potentially contributing to sexual dimorphism in programming events.

Finally, maternal circulating levels of adiponectin, secreted from maternal adipose tissue, are inversely correlated with maternal BMI or FM (263). The action of adiponectin in peripheral tissues, such as muscle, is to increase insulin sensitivity, and the loss of this sensitizing agent with increasing adiposity promotes insulin resistance associated with obesity (264). Contrary to muscle, adiponectin inhibits insulin signaling in the placenta through the activation of PPARα, a transcription factor that increases ceramide synthase expression, resulting in increased intracellular ceramide and inhibition of IRS-1 (265). High adiponectin in lean mothers inhibits insulin-stimulated placental nutrient uptake and results in greater allocation of resources to the mother. The opposite occurs in obese women who have high insulin levels and low adiponectin, both of which promote nutrient transfer to the fetus (266). In fact, there is an inverse correlation between maternal adiponectin and birth weight, suggesting that this is an important maternal resource allocation mechanism to modulate the impact of insulin on placental function and fetal growth

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in accordance with maternal nutrient status (172, 267). Supplementation with adiponectin during the final 4 days of pregnancy in high-fat/high-sugar diet-induced obese pregnant mice prevented excess placental nutrient transfer, returned transporter expression to control levels, and prevented fetal overgrowth. Adiponectin supplementation that prevents intrauterine overgrowth in obese dams ameliorates developmental programming of metabolic disease. For example, adult offspring of obese dams who were maintained on normal chow after weaning demonstrated characteristic programming of cardiovascular and metabolic disease including obesity, glucose intolerance, hypertriglyceridemia, liver steatosis, and cardiac diastolic dysfunction. Yet adult offspring of the adiponectin-supplemented obese dams in the third trimester did not present with any of these cardio-metabolic programming events (268, 269). Collectively, these studies suggest that therapeutic strategies directed at placental function to normalize fetal growth without changing the overall phenotype of the mother are sufficient to prevent programming of adult metabolic disease in maternal obesity. Whether or not they can be employed in IUGR pregnancies to ameliorate long-term metabolic disease in postnatal life is the focus of future research studies.

2.4. Placental Epigenetic Regulation in DOHaD

In EPIDEMIOLOGY OF THE DEVELOPMENTAL ORIGINS OF ADULT HEALTH AND DISEASE, the role of maternal diet in methylation patterns of key metabolic genes was discussed as a potential mechanism linking in utero growth restriction and metabolic diseases in the offspring (8, 100, 202). It is therefore of great relevance that multiple signaling pathways controlling key functions of the human placenta are subjected to epigenetic regulation. Given that epigenetic modifications of DNA in the fetus may contribute to poor metabolic health later in life (270), differential methylation patterns of placental tissue may serve as an early indication of the severity of the programming events in utero.

After methylation erasure in gamete formation and during the blastocyst stage of development, the reestablishment of methylation patterns in the trophectoderm is distinct from the inner cell mass (271). This early phase of development with dramatic changes in methylation is particularly sensitive to environmental and nutritional influences, and given that the placenta is one of the first organs to develop, epigenetic regulation of gene expression likely contributes to trophoblast invasion along with anatomical and functional changes across gestation (272). Although in general trophoblast DNA is mainly hypomethylated, trophoblast DNA also contains a large number of imprinted or monoallelic genes, due to hypermethylation of either the maternal or paternal allele that silences its expression (273). Many of the >100 genes that have been shown to be imprinted in the placenta are involved in the regulation of placental growth and function, including nutrient transport, collectively modulating fetal growth (274). Paternally expressed genes tend to enhance fetal growth potential, whereas maternally expressed genes tend to limit growth, consistent with the conflict hypothesis of imprinted mammalian genes (275, 276). As well, alterations in maternal nutrition and metabolism regulate the expression of both placental and fetal genes by epigenetic mechanisms (277).

The expression of numerous imprinted genes in the human placenta is subjected to regulation across gestation and is associated with fetal growth. Moore and coworkers (278) collected chorionic villous samples (CVS) at 11–13 wk, as well as term villous tissue, to examine the expression of placental imprinted genes and fetal growth across gestation. Paternally expressed IGF-2 and IGF-2 receptor genes in CVS correlated with crown-rump length in early gestation and birth weight at term, but placental expression of these genes at term was not related to size at birth. The expression of maternally imprinted pleckstrin homology-like domain family A (PHLDA) at 12 wk was not associated with early fetal growth, whereas term placenta expression was negatively correlated with birth weight. Likewise, term placental expression of maternal imprinted gene growth factor receptor-bound protein 10 (GRB10) was negatively correlated with head circumference. Expression of the paternally imprinted delta-like 1 homolog (DLK1) was correlated with growth in both early and term gestation (278). Two human growth syndromes exemplify the significance of placental genomic imprinting. It is noteworthy that in the developmental disorder Silver–Russell syndrome, which is characterized by stunted growth and limb or facial asymmetry, 40–60% of cases are due to the imprinted cluster on chromosome 11p15.5 containing the telomeric IGF2/H19 domain, which is controlled by parentally methylated imprinting control region 1 (ICR1). Hypomethylation of ICR1 upstream of IGF2/H19 controls the reciprocal imprinted expression of the paternally expressed growth-promoting IGF2 gene, resulting in lower IGF-2 expression, leading to fetal growth restriction and smaller, underdeveloped chorionic villi in the placenta (279, 280). Conversely, Beckman–Wiedemann syndrome, which exhibits hypermethylation in the imprinting control region of the IGF2 gene, is characterized by fetal overgrowth (281).

To determine associations between placental differential methylation and human intrauterine growth, both genomewide methylation studies and targeted gene

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approaches have been conducted. Results of these studies have been inconsistent, perhaps because of small sample size and failure to account for key confounding factors (282). Additionally, polymorphic DNA methylation is a characteristic of imprinted genes in humans and suggests a complex interindividual, tissue-specific variation contributing to a lack of clear methylation/expression concordance in imprinted placental genes. (283). In one study, IUGR was associated with 22 differentially methylated regions (DMRs) in human placenta (284), which were highly predictive of IUGR. However, in a whole genome methylation study no differentially methylated positions were found in placentas of growth-restricted versus normal-size infants (285). Recently, Devaskar and colleagues (286) found >500 differentially methylated genes in CPG islands in placenta from IUGR compared with normally grown and LGA babies. The differentially methylated regions were distinct for each birth weight group studied, suggesting a role for epigenetic regulation of the placenta associated with fetal growth rates. The genes impacted affected critical placental functions such as nutrient transfer, hormone synthesis, and metabolism. Interestingly, the placenta may also contain information about future postnatal disease risk, given that genes associated with cardiometabolic disease were differentially methylated in the placenta in a birth weight-dependent manner (286).

Several factors investigated in the etiology of IUGR have been demonstrated to influence epigenetic regulation of the placenta. For example, maternal health status, such as psychosocial stress, has been associated with differential genomewide placental methylation (287). High levels of maternal stress resulted in divergent methylation patterns in genes coding for metabolic pathways including AKT/PI3K. Moreover, maternal metabolic health, including dyslipidemia, impacts methylation of PPAR genes in placenta and in key organs of the offspring (288). PPARs are key transcription factors that act as central regulators of lipid metabolism, and differential methylation that occurs in utero is believed to contribute to lifelong health risk. Another nutrient-responsive system in the placenta is the OGT or *O*-linked *N*-acetylglucosamine (*O*-GlcNAC) enzyme that catalyzes the addition of *O*-linked *N*-acetylglucosamine to serine and threonine residues in intracellular proteins that regulate placental function due to the loss of regulatory phosphorylation sites. Histone proteins, which are critical for modulating gene expression, are regulated by *O*-GlycNAcylation (289). Placental OGT is differentially expressed in males and females and may represent one of the underlying mechanisms of sex differences in intrauterine programming. In mice, increased stress during pregnancy resulted in a sex-dependent programming of male hypothalamic-pituitary axis, and placenta-specific knockout of the OGT reversed this phenotype (290).

In summary, there are a number of key metabolic and physiological processes that support placental sufficiency and allow healthy fetal growth and development to occur. However, when challenges to placental development or functioning occur, significant effects on the fetus, leading to both acute and chronic adaptations, may be detrimental for postnatal health. Moreover, the placenta does not function independently of maternal physiology and fetal development, and complementary actions imparted by maternal health can add additional insult to a compromised placenta. Therefore, it is clear that a number of processes likely underlie the interactions between the above-discussed relationship between maternal nutritional state (BMI, famine, dietary constraints or excesses, stress, and epigenetics) and birth weight outcomes and long-term health. Although these processes provide a short-term survival advantage to produce a smaller, but viable, fetus, the programming of metabolic disease later in life is a serious long-term consequence.

3. ADVERSE IN UTERO ENVIRONMENT AND METABOLIC DISEASE

As reviewed in EPIDEMIOLOGY OF THE DEVELOPMENTAL ORIGINS OF ADULT HEALTH AND DISEASE, a large number of epidemiological studies have demonstrated that a number of maternal and paternal factors, such as obesity, exposure to poor nutrition, and famine, are associated with a higher risk of chronic diseases in the offspring. Moreover, as ROLE OF THE PLACENTA IN FETAL GROWTH AND METABOLIC DISEASES nicely illustrates, the impact of these external insults, whether occurring during preconception and/or during gestation, can first be measured upon placental functioning. The placental deficiency (i.e., altered nutrient sensing, nutrition transfer, and/or endocrine function) that ensues ultimately culminates in compromised fetal development. This section provides the latest insights from human and animal studies linking fetal growth restriction with adverse postnatal metabolic outcomes, including dysglycemia, dyslipidemia, fatty liver disease, and cardiovascular dysfunction. Regardless of the prenatal environment leading to placental insufficiency and IUGR, rapid postnatal catch-up growth may exacerbate the incidence and severity of these metabolic deficits.

3.1. Developmental Influences on Dysglycemia

Although over 20 years has passed since David Barker first published the seminal findings that impaired fetal growth is associated with a greater risk of developing diabetes, obesity, and hypertension, we are only now elucidating the underlying mechanisms for these programmed

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metabolic deficits (291). Importantly, recent clinical reports such as the EPOCH study have reaffirmed Barker's findings by demonstrating that IUGR children exhibit postnatal catch-up growth leading to higher circulating insulin levels, greater homeostatic model assessment of insulin resistance (HOMA-IR), and lower adiponectin levels in childhood independent of other maternal or childhood factors (292). As T2D is first characterized by early decreases in insulin sensitivity, augmented insulin resistance, and impaired insulin secretion, it is not surprising that all of these characteristics are exhibited early in SGA or IUGR offspring (293). First, IUGR offspring exhibit hypoglycemic hyperinsulinism as early as birth, with a progression of insulin resistance over the first 3 yr of life (294–298). The reduced insulin sensitivity in these offspring can be attributed, in part, to altered skeletal muscle fiber composition that began in utero and is maintained later in life (299). Second, this impaired insulin sensitivity is worsened in SGA offspring with postnatal catch-up growth compared with SGA offspring without catch-up growth or appropriate-for-gestational age (AGA) offspring (300–302). Third, HOMA-IR studies have observed associations between birth weight and β-cell function in later life (295, 303). Although the incidence of IUGR and its corresponding relationship to long-term dysglycemia have remained steadfast over these decades, to date there are no reliable biomarkers for predicting the threat of a poor in utero environment (304). However, advances in metabolomics are beginning to uncover markers such as myoinositol in IUGR newborns, which is linked to glucose intolerance and insulin resistance in adulthood (305, 306), but there is still debate as to whether myoinositol would be a predictive biomarker in utero (306, 307).

To date, although several animal models (i.e., maternal glucocorticoid exposure, protein or caloric restriction, and hypoxemia) exist to model the etiology of fetal growth restriction on the developing pancreas and long-term dysglycemia, we focus our review on the role of maternal uterine ligation in long-term metabolic syndrome (308, 309) first and foremost because placenta-induced IUGR afflicts ~5% of pregnancies and represents the main cause of IUGR in the Western world (308, 310, 311). Second, given that placental insufficiency-induced IUGR leads to decreases in oxygenation and substrate availability for the fetus (312–314), the uterine ligation (or ablation) model serves as an excellent model for examining the impact of idiopathic IUGR on postnatal metabolic disease. In **FIGURE 6** we present an overview of the impact of placental insufficiency on metabolic organs in postnatal life. The permanent ligation of both uterine arteries leads to hypoxia, hypoglycemia, and decreased availability of growth factors (315, 316). Doppler analysis has confirmed that this model mimics the hemodynamic features of the human IUGR fetus particularly in the ductus venosus (317). In rats, uterine ligation leads to development of the metabolic syndrome in the offspring including type 2 diabetes (i.e., reduced β-cell mass), dyslipidemia, and hypertriglyceridemia (318–320). Moreover, several of these metabolic defects are reciprocated into the F_2 generation (321, 322). Elegant studies by Park et al. (323) have demonstrated that uterine-ligated IUGR offspring develop type 2 diabetes because of epigenetic silencing of the critical β-cell transcription factor Pdx-1. Interestingly, the development of glucose intolerance in these IUGR offspring could be ameliorated with the use of Exendin-4 (a GLP analog) in neonatal life to restore Pdx-1 expression and islet vascularity (324, 325). Other long-term IUGR-induced pancreatic defects (e.g., at 6 mo of age) included irregular shape, increased macrophage-induced inflammation, fibrosis, and hemosiderosis, and these effects were enhanced by a high-fat postnatal diet (326). Some of these pancreatic defects can be observed in the second generation, as IUGR female offspring bred to control males led to impaired first-phase insulin signaling in both sexes of the F_2 generation, with sex-specific changes in β pancreatic cell mass (322). Aside from pancreatic defects, the glucose intolerance in these IUGR offspring can also be attributed to defects in insulin target organs including the muscle, adipose, and liver. In the muscle, uterine-ligated IUGR offspring exhibit defects in mitochondrial activity and insulin receptor function in muscle, but this was demonstrated to be dependent upon litter size and sex (327, 328). With respect to adipose, very little is known regarding insulin receptor function in uterine-ligated offspring; however, aged females do exhibit higher lipogenesis due to increased adipose fatty acid synthase and endoplasmic reticulum (ER) stress (329). Interestingly, IUGR liver deficiencies contributing to insulin resistance include altered glucose transporter expression, impairment of fatty acid metabolism, increased glucocorticoid activity, augmented gluconeogenesis, and blunted insulin suppression (318, 319, 330–332). These IUGR offspring also exhibit decreased hepatic and circulating insulin growth factor 1 (Igf-1), which is critical for insulin function, glucose metabolism, and growth (333).

3.2. In Utero Growth and Dyslipidemia

Barker's early studies (334) demonstrated that there was a strong correlation between reduced abdominal circumference at birth and elevated total and LDL cholesterol in adulthood. Since that time, elegant studies by Singhal et al. (335) have indicated that catch-up growth in neonatal life, likely due to growth-promoting formula diets, is associated with an exacerbation of the incidence and onset timing of dyslipidemia (e.g., higher LDL-to-HDL ratio) in IUGR infants. Alterations in circulating cholesterol acceptors in the sera of IUGR offspring

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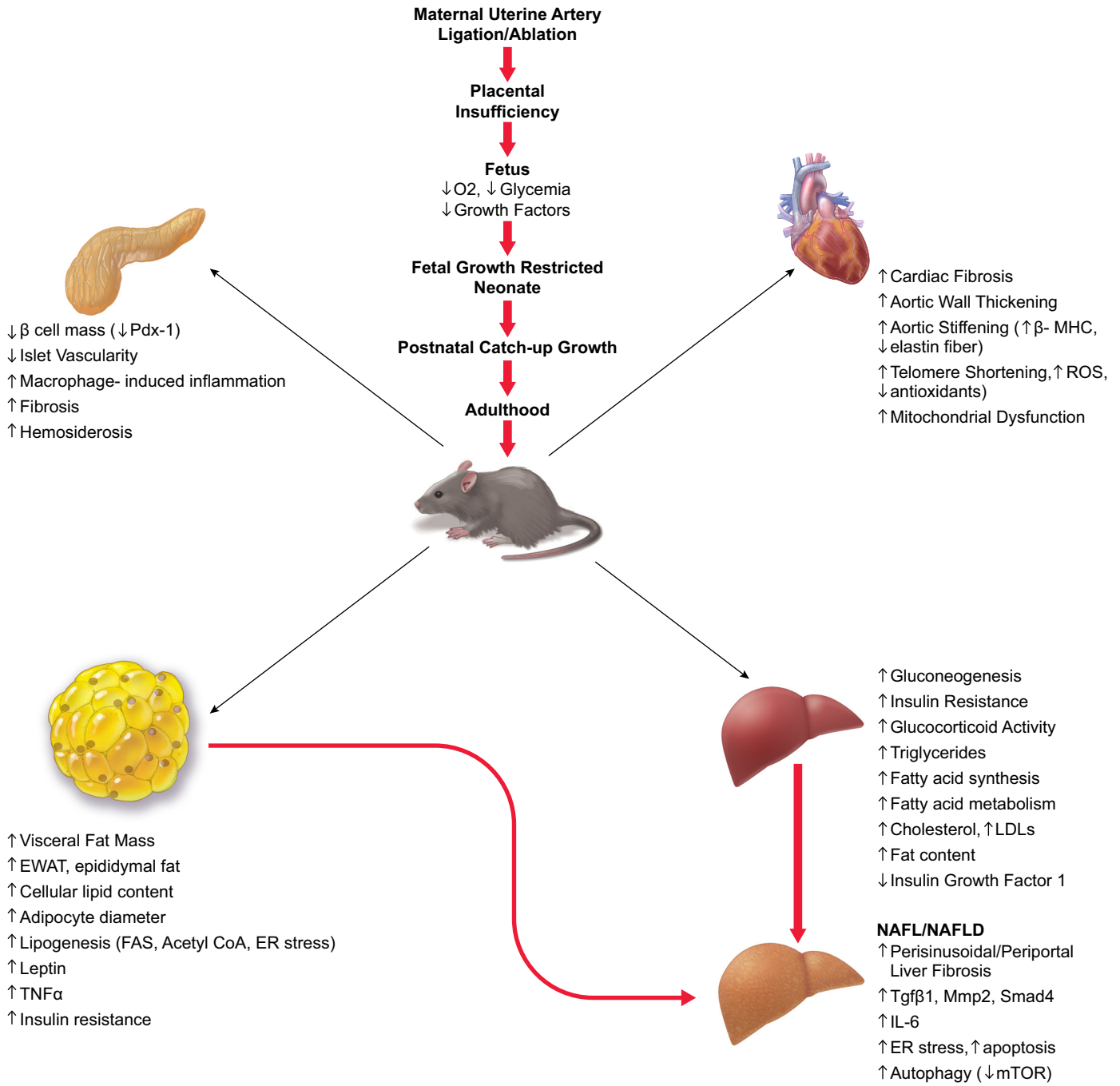

FIGURE 6. Summary of the metabolic deficits exhibited in the fetal growth-restricted offspring from dams exposed to uterine artery ligation/ablation. ER, endoplasmic reticulum; EWAT, epididymal adipose tissue; MHC, myosin heavy chain; mTOR, mechanistic target of rapamycin; ROS, reactive oxygen species.

have also been speculated to underlie the reduced cholesterol efflux observed, an indicator of early atherosclerosis long before clinical diagnosis (336). Further evidence that cholesterol homeostasis is impaired early in life is evident from a study of 55 SGA children in which half of them were in the highest quartile for serum total cholesterol of the AGA children at 12 yr of age (337). Interestingly, poor catch-up growth with respect to height, female sex, and early pubertal stage all predicted high cholesterol in these SGA children (337). However, a 2004 systematic review of 79 published studies concluded that impaired fetal growth does not influence long-term blood circulating cholesterol levels to the extent that it would actually increase vascular disease risk (338). It should be noted that within those studies significant heterogeneity was attributed to strong associations observed in several small clinical studies. Another limitation of these studies is the fact

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that birth weight was used as the only indication of fetal growth restriction. A study from The Netherlands indicated that greater first-trimester fetal crown-to-rump length is associated with lower total and LDL cholesterol, android-to-gynoid FM ratio, and blood pressure in children aged 5–7 yr (339). However, there were no correlations between first-trimester fetal crown-to-rump length and other cardiovascular outcomes (339). With respect to triglycerides, across several studies fetal growth has been inversely associated with fetal and postnatal circulating triglycerides (248, 340, 341). One exception is the Aboriginal Birth Cohort Study of 11-yr-old children (1987–2001), which identified that circulating triglycerides levels were associated with current child weight but not birth weight (342). Moreover, although blood pressure in that study was inversely proportional to birth weight, this relationship was further strengthened when adjusted for current child weight (342). A recent analysis of Turner syndrome offspring, who are frequently born with low birth weight and undergo greater weight gain in postnatal life, identified strong links between fetal growth and dyslipidemia. In these offspring, there was a significant negative correlation between birth weight and lipid profiles (e.g., cholesterol and triglycerides) along with HOMA-IR (343).

Animal studies utilizing uterine ligation in baboons to mimic placental insufficiency-induced IUGR revealed that female offspring exhibited higher cholesterol, LDL levels, and subcutaneous fat at 8–9 yr (human equivalent of 32–36 yr), whereas male offspring displayed increased pericardial fat deposition (344). High hepatic and circulating serum cholesterol is also observed in uterine-ligated female rat offspring because of decreases in hepatic Cyp7a1, the critical enzyme in cholesterol catabolism (345). Although the mechanism for this was not fully elucidated, others have demonstrated that long-term silencing of *Cyp7a1* in low-birth-weight rat offspring is due to repressive histone modifications that originate in fetal life (346). Aside from changes in cholesterol, male guinea pig IUGR offspring from maternal uterine ligation demonstrate greater epididymal adipose tissue (EWAT), epididymal fat cellular lipid content, and mean epididymal adipocyte diameter by adulthood (347). Similar to what has been observed in the pancreas, IUGR elicits dyslipidemic effects across generations, as F_2 IUGR rats display increased central FM, elevated triglycerides and LDLs, along with higher fatty acids (321). Interestingly, supplementation of the F_1 generation IUGR offspring with essential nutrients (i.e., folic acid, choline, vitamin B_{12}, betaine, L-methionine, L-arginine, and zinc) prevented the dyslipidemia in both sexes of the F_2 generation due to amelioration of IUGR-induced DNA methylation of the promoter of *Igf-1* (321).

3.3. Intrauterine Growth Restriction and Nonalcoholic Fatty Liver Disease

Over time, dyslipidemia in the liver can develop into liver fibrosis [i.e., nonalcoholic fatty liver (NAFL)/nonalcoholic fatty liver disease (NAFLD)], and ultimately ~20% of those patients develop end-stage cirrhosis (348). Collectively, liver fibrosis is thought to underlie up to 45% of deaths in the developed world (349, 350). In a multicenter, cross-sectional study, both low- and high-birth-weight children had a greater risk of developing NAFLD (351). An Italian study also found a fourfold higher incidence of pediatric NAFLD in IUGR children, independent of insulin resistance (352). Interestingly, low-birth-weight children had greater odds of developing severe advanced fibrosis, whereas high-birth-weight children were more prone to hepatic steatosis (351). Furthermore, postnatal catch-up growth in the first 6–12 mo of life in SGA prepubertal children was demonstrated to increase the incidence of NAFLD (353), and insulin resistance was significantly correlated to liver steatosis (353).

These observations in humans are nicely replicated in animal models of IUGR. The uterine-ligated guinea pig dam leads to IUGR offspring exhibiting perisinusoidal or periportal fibrosis in the liver accompanied by expression of profibrotic markers including *Tgfb1*, *Mmp2*, and *Smad4* (354). The IUGR-mediated fibrosis may stem early from dyslipidemia, given that uterine ligation leads to an increase in overall and hepatic fat content early in fetal life (355). Moreover, uterine-ligated IUGR mouse pups exhibit higher visceral FM, fasting blood glucose, and leptin concentrations (356). Aside from the dyslipidemia observed, uterine-ligated IUGR offspring also display hepatic insulin resistance at 8 wk, well before any evidence of system insulin resistance from 3 to 6 mo (357). This was due, in part, to suppressed IRS-2 and Akt1 phosphorylation in the liver along with higher expression of the gluconeogenic enzymes PEPCK and G6Pase (357). Similar increases in both hepatic lipids and insulin resistance are also observed in maternal hypoxia-induced IUGR offspring (358). As adipose dysfunction and inflammation are involved in the etiology of NAFLD, it is noteworthy that IUGR rat offspring at 6 mo of age exhibit greater de novo fatty acid synthesis in adipose tissue due to increased acetyl-CoA and fatty acid synthase expression (359). In addition, male IUGR rats at 3 wk of age display high circulating and adipose TNF-α, an early hallmark of NAFLD (360). Moreover, spontaneous IUGR piglets with a postnatal high-fat diet have increased hepatic IL-6 mRNA later in life, suggesting increased local inflammation (98).

Although the contributions of growth restriction followed by a poor postnatal diet need to be better investigated in animal models, one study has demonstrated

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that maternal caloric restriction in mouse dams, followed by a postnatal high-fat diet, results in low-birth-weight offspring with an increased incidence of hepatic steatosis coupled with greater infiltration of liver macrophages (361). However, the contributions of IUGR alone on a normal postnatal diet were not examined. Interestingly, these hepatic defects were ameliorated with treatment of tauroursodeoxycholic acid (TUDCA), a known inhibitor of ER stress (361). This suggests that IUGR followed by postnatal high-fat diet may play a role in ER stress-mediated NAFLD, although postnatal catch-up growth of the liver could also be a contributing factor (362). In addition to ER stress, hepatic apoptosis in NAFLD has been attributed to the liver's inability to proceed through autophagy, the process of lysosome-mediated cell degradation (188). This suggests that the intrauterine environment may play an early role in setting the stage of NAFLD in postnatal life, given that IUGR piglets exhibited reduced factors (i.e., mTOR, protein phosphatase 2A) associated with hepatic autophagy (363). This hypothesis is further substantiated by that fact that idiopathic IUGR is associated with greater fatty acid transporters in the placenta (183). Although this review is mainly focused on how placental insufficiency-induced IUGR drives long-term hepatic defects, it is noteworthy that ethanol- or caffeine-induced IUGR in rats also results in offspring with greater incidence of NAFLD (364, 365). Moreover, other complications in pregnancy including maternal obesity or gestational diabetes are also associated with fatty liver disease in postnatal life (366, 367).

3.4. Intrauterine Growth Restriction and Cardiovascular Disease

Although the principles of Barker's initial hypothesis were challenged as socio-economic and lifestyle factors were not accounted for in the relationship between fetal growth and the incidence of cardiovascular disease, more recent studies that do statistically adjust for occupation, education, income, and childhood/adult socio-economic status have minimized those concerns (291, 368–371). With respect to birth weight or blood pressure, a number of studies corroborate Barker's findings for both sexes, and across ethnic/racial groups, location, and age (369, 372–374). It has also been reported that for a 1-kg increase in birth weight there is ~2 mmHg lower systolic blood pressure from neonatal life to adulthood (341, 375, 376). However, caution is recommended in interpreting these data, given that such a magnitude of change would never be high enough to fully explain the clinical hypertension observed in Barker's early findings. Clearly, other underlying indexes must also contribute to long-term cardiovascular complications exhibited in these growth-restricted offspring. More recent studies have identified that a higher ratio of apolipoprotein B to apolipoprotein A-I (Apo A1) in fetal plasma, a predictor of atherosclerosis, is elevated in IUGR offspring, uncovering an early link between an adverse fetal environment and cardiac health (377). Elegant Doppler studies have revealed that myocardial performance index (MPI) is elevated in IUGR fetuses with end-diastolic blood flow (EDF) and is further progressed with greater hemodynamic compromise and fetal deterioration even while maintaining cardiac output (378). B-type natriuretic peptide, a well-established predicator of heart failure, was also increased in IUGR fetuses in a severity-dependent manner (378, 379). Doppler studies have further revealed that SGA and IUGR infants exhibit higher blood pressure and carotid intima-media thickness at 3–6 yr of age (380). With respect to the contribution of postnatal catch-up growth, Eriksson and colleagues (381) have demonstrated in a Finnish longitudinal study that rapid weight gain within 1 yr increases the risk of coronary heart disease later in life. However Tzschoppe et al. (382) have shown that an increase in carotid intima-media thickness is demonstrated in IUGR infants at 6 mo irrespective of postnatal catch-up growth and even in the absence of elevated blood pressure. Moreover, IUGR children have more globular hearts and impaired stroke volume, which is compensated by higher heart rates and diastolic changes in infants when the IUGR was early onset (380). In contrast, late-onset IUGR infants displayed higher stroke volume and cardiac output (380). Other studies have linked IUGR outcomes with high aortic intima-media thickness at birth (186, 383, 384). Skilton et al. (385) further demonstrated that the adverse effects of impeded fetal growth on arterial wall thickening could be prevented with dietary ω–3 fatty acid supplementation during the first 5 yr of postnatal life. The first few years of postnatal life may be particularly critical in IUGR offspring, given the stronger associations made between postnatal catch-up growth and long-term blood pressure, irrespective of birth weight (386–388). This is in contrast to maternal obesity-induced cardiac dysfunction in postnatal life (389), where it has been demonstrated in mice born to obese dams that the postweaning diet does not influence the risk of cardiac disease (390).

To date, animal models have shed some light on the underlying mechanisms for the in utero programming of cardiac dysfunction including reduced antioxidants, telomere shortening, mitochondrial dysfunction, reactive oxygen species (ROS) damage, and epigenetic modifications (391). Uterine ligation in guinea pig dams leads to IUGR offspring with increased cardiac fibrosis and aortic wall thickening by adolescence (392). In adulthood, it was further demonstrated in guinea pigs that IUGR has a greater impact on long-term aortic stiffening compared with a postnatal high-fat diet or vehicle controls (393). This is partially explained by the fact that elastin fiber content was

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decreased in these IUGR guinea pig fetuses by 14%, followed by a 51% reduction in adulthood (394). Moreover, the central stiffness observed in these IUGR offspring might also result from changes in expression of myosin heavy chain β (β-MHC), a marker of cardiac remodeling (394). β-MHC was also sixfold higher in these IUGR fetuses and threefold higher in IUGR offspring (394).

Although decades of epidemiological and animal studies have further established Barker's observations of an association between a poor in utero environment and long-term metabolic disease, the present review updates its impact on dysglycemia, dyslipidemia, fatty liver disease, and adverse cardiovascular outcomes. Although the animal studies seem to be fairly consistent, there are several examples from clinical studies in which discrepancies exist in predicting a poor postnatal outcome resulting from IUGR. These discrepancies may exist because of differences in the postnatal environment. Clearly, further studies are warranted to address how management of postnatal catch-up growth could ameliorate these metabolic deficits. More importantly, early screening and reliant predictors of IUGR will result in efficacious strategies to reduce the impending threat of impaired fetal growth.

4. IN UTERO ENVIRONMENTAL CHEMICALS AND METABOLIC DISEASES

Thus far, this review has focused on cohort studies of human growth, in utero and early childhood, that may influence the development of metabolic disorders. Clearly, abundant evidence of fetal programming of metabolic function has been presented that identifies key maternal-fetal-placental mechanisms that may put growth-restricted fetuses at increased risk of future disease. In the modern environment, the potential for in utero disruption of metabolic development is further compounded by the thousands of chemicals present in our environments, many of which readily enter the maternal circulation, cross the placenta, and alter fetal hormone production, tissue development, and gene expression. In this section we review epidemiological and experimental evidence on prenatal exposure to environmental chemicals in relation to obesity, glucose, and lipid dysregulation and discuss special considerations and future directions for this emerging field.

4.1. Overview of Environmental Metabolism-Disrupting Chemicals

It has been long known that chemical exposures during pregnancy can have profound and irreversible effects on fetal development. The infamous examples of limb malformations following thalidomide administration and neurotoxic symptoms of Minimata disease resulting from methylmercury exposure provide incontrovertible evidence of fetal vulnerability to environmental exposures (395, 396). More recently, it has become clear that in utero chemical exposures may impact health and disease risk in more subtle ways as well. Indeed, a wide range of environmental chemical exposures can alter the intricately coordinated developmental processes underlying fertilization, cellular differentiation, organogenesis, and fetal development. Developing organisms are at even greater risk given the lack of mechanisms (e.g., detoxifying enzymes, DNA repair mechanisms, blood-brain barrier) that may offer greater protection from chemical exposures in mature individuals (397).

In contrast to the examples of overt toxicity described above, more often, environmental exposures have subtle developmental impacts. One timely example is the role of environmental exposures in the modern epidemic of obesity and metabolic diseases, first proposed in 2002 by Baillie-Hamilton (398) after observing the parallel temporal rises in environmental pollutants and obesity. In the nearly two decades since then, considerable research has examined the "obesogenic" effects of a wide range of environmental chemicals in vitro, as well as in animal models and humans (399). Informed by growing evidence that obesity cannot be fully explained by an imbalance between caloric intake and expenditure, Blumberg and Grün's (399) obesogen hypothesis proposed that environmental chemicals could promote obesity, particularly when exposure occurred during critical developmental periods. A number of potential pathways were identified as vulnerable to disruption including, but not limited to, *1*) adipocyte commitment, differentiation, and storage; *2*) basal metabolic rate and metabolic "set points"; and *3*) regulation of food intake (**FIGURE 7**). In 2015, the Parma Consensus Statement proposed a broader metabolism-disrupting chemical (MDC) hypothesis, suggesting that, in addition to obesity, chemical exposures may drive metabolic changes, such as insulin resistance and β-cell death, that ultimately contribute to metabolic diseases (400).

A primary mechanism of MDC action is through endocrine disruption and indeed, many MDCs are well-documented endocrine disruptors. By definition, endocrine disruptors alter homeostasis or action of endogenous hormone systems. Even transient exposures during critical developmental periods may permanently reprogram the endocrine axes that regulate weight and metabolism, leading to lifelong changes in physiology and disease risk (401). Endocrine disruptors can act on hormone systems in numerous ways, including changing the synthesis, release, transport, metabolism, activity, and elimination of key hormones. Thus far the preponderance of research on endocrine disruptors has focused on disruption of estrogen, androgen, and thyroid activity (402), all of which contribute to the regulation of adipogenesis,

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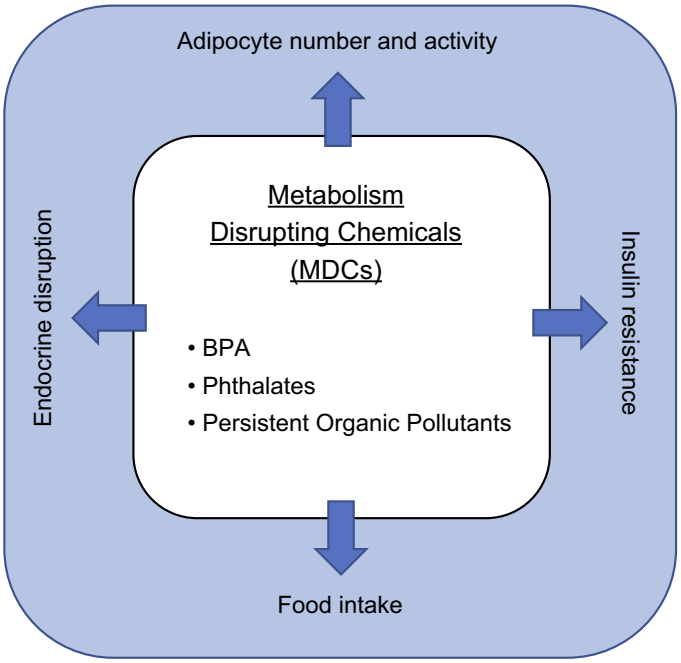

FIGURE 7. Proposed mechanisms by which metabolism-disrupting chemicals may contribute to metabolic diseases. BPA, bisphenol A.

as well as satiety and energy balance (397). For example, production of estradiol, which is important in the regulation of β-cell insulin secretion, may be disrupted by multiple chemicals including bisphenol A (BPA), phthalates, and phytoestrogens (249, 403). Although less well studied, other endocrine pathways involving important metabolic regulators in the gastrointestinal tract (ghrelin, cholecystokinin, glucagon-like peptide-1), pancreas (insulin, glucagon), muscle (insulin), liver (glucagon, insulin, FGF21), adipose tissue (leptin, adiponectin), and brain (neuropeptide Y, proopiomelanocortin) (397) may also be vulnerable to disruption by environmental chemical exposure. Endocrine disruptors can interact with a wide range of nuclear receptors, moreover, including those that are essential for metabolic development and regulation such as aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and constitutive androstane receptor (CAR), providing additional support for a link between endocrine and metabolic dysregulation (404). Although exposure to MDCs is unlikely to cause metabolic disease or obesity independently, by altering relevant hormonal pathways these chemical exposures may predispose individuals to adipose tissue accumulation, metabolic dysregulation, and weight gain by potentiating the risks of known metabolic risk factors such as caloric excess, circadian dysregulation, or physical activity (405).

4.2. Exposure to MDCs

At present, >85,000 registered chemicals are in production worldwide (406). Although most of these chemicals have not been extensively studied to understand their health impacts, ~1,000 have been identified as endocrine disruptors (407, 408). Of these, it is likely that a large proportion can be classified as MDCs. For many compounds, environmental exposure is widespread in the general population because of their frequent use in consumer products and industrial applications (409–411). Depending on the particular chemical, there may be multiple routes of exposure, including inhalation of polluted air or contaminated dust, absorption through the skin from MDC-containing personal care products (such as lotions, cleansers, sunscreens, and cosmetics), or ingestion of contaminated water and food. As many MDCs can be transported long distances in air or water, they have been found all over the world including in remote locations and populations (412–415). As a result, for many potentially MDCs, such as BPA and phthalates, exposure is near universal, meaning that identifying an unexposed "control" population is impossible. It also means that typically people are concurrently exposed to a mixture of MDCs, which is important when considering potentially additive or synergistic health impacts (416–418). For example, in a study of children participating in the U.S. National Health and Nutrition Examination Survey (NHANES), 81% of chemicals studied (26 of 31) were detectable in >90% of subjects (419). Similarly, a study of pregnant NHANES participants measured 163 synthetic chemicals from 12 different classes, finding that 99–100% of participants had detectable levels of 8 of the 12 chemical classes studied (418). Most of the chemicals

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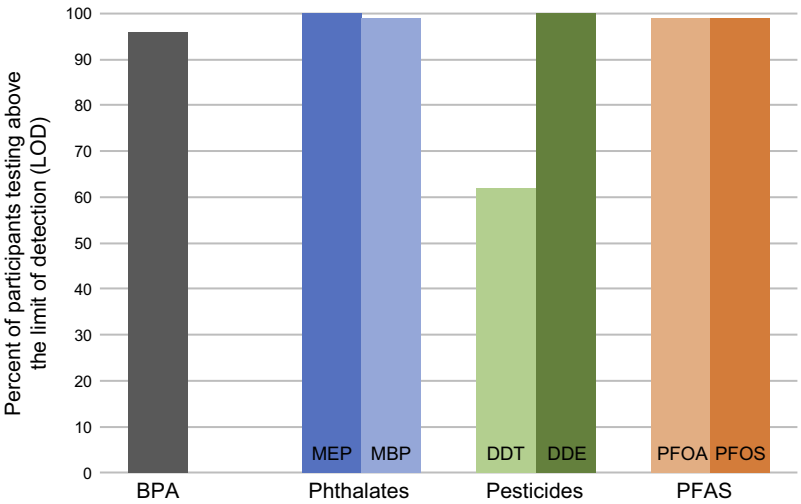

FIGURE 8. Ubiquitous exposure to select metabolism disrupting chemicals among pregnant women in National Health and Nutrition Examination Survey (NHANES). BPA, bisphenol A; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; MBP, monobutyl phthalate; MEP, monoethyl phthalate; PFAS, perfluoroalkyl substance; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

included in these analyses were suspected MDCs, including perfluoroalkyl substances (PFASs), polybrominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, phthalates, phenols, and polycyclic aromatic hydrocarbons, providing further evidence of widespread exposure in the general population, including pregnant women (**FIGURE 8**). Importantly, these chemicals are also detectable in cord blood and/or amniotic fluid, moreover, indicating widespread fetal exposure (420–423). Even within highly exposed populations, however, individual body burden may vary by an order of magnitude or more, depending on factors such as personal care products used, consumption of processed foods, and use of plastics, providing the variation needed to explore the relationship between these exposures and metabolic outcomes.

With dozens (if not hundreds) of suspected MDCs, it is impossible to comprehensively review their potential to impact metabolic disease. Instead, we focus on a small number of exemplar chemicals that are the subject of ongoing basic science and epidemiological study in the context of metabolic dysregulation, including BPA, phthalates, organochlorine pesticides, and PFASs as summarized in **TABLE 3**. These are among the chemicals identified as potentially strong candidate contributors to the obesity epidemic in a 2012 National Toxicology Program meeting on Environmental Chemicals in Diabetes and Obesity (424). Environmental exposure to these chemicals in the general population is widespread, thus presenting a public health challenge as well as, potentially, an opportunity to intervene through large-scale policy and/or behavioral changes. For each of these chemicals, considerable mechanistic work in animal models has been conducted, yet variation in timing of exposure as well as dose (with older studies often using supranormal doses that far exceed typical human environmental exposures) presents challenges when translating results to humans (401). Inflammation, oxidative stress, and mitochondrial mechanisms are all important candidates for disruption by MDCs, and, importantly, multiple mechanistic pathways may be simultaneously impacted by the same MDC exposure, resulting in a metabolic syndrome-like phenotype rather than targeted effects on individual organ systems (397).

4.2.1. Bisphenol A.

Despite public outcry over its use in the manufacture of baby bottles and reusable plastic water bottles in the 2000s, BPA is still in widespread production, with >15 billion pounds produced annually (425). BPA is most commonly used to make polycarbonate plastics and epoxy resins, and it is widely found in consumer products including DVDs, eyeglasses, food packaging including canned foods, medical equipment, and thermal receipt paper (426). Given that BPA can readily leach from plastic products including epoxy can linings into surrounding media, the potential for inadvertent contamination of food and drink is high and accounts for the vast majority of human exposure (427). Thus although BPA is rapidly metabolized in the body (half-life: 4–5 h), exposure is virtually continuous, and in NHANES BPA was detected in the urine of 92.6% of participants (428). Best known for its estrogenicity (429), BPA's interference in additional pathways, including glucocorticoid, thyroid, and PPARγ systems, may also contribute to metabolic disruption (430). Of all of the purported MDCs, BPA has been most extensively studied, with a large body of in vitro, experimental animal, and epidemiological work examining developmental exposure in relation to glucose tolerance, insulin resistance, β-cell function, and hepatic steatosis as well as weight gain and body size (397, 401).

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Table 3. ***Chemical classes with suspected metabolism disrupting impacts during development***

Chemical	Half-Life in Human Body	Major Sources	Summary of Epidemiological Evidence	Potential Mechanisms
Bisphenol A (BPA)	Several hours	Food, thermal receipts, medical/dental devices, DVDs and CDs, electronics, epoxy resins, polycarbonate plastics	Mixed evidence linking prenatal BPA to higher child BMI and adiposity; possible effect modification by sex	Enhanced adipogenesis and lipid storage; impaired glucose utilization; promotion of oxidative stress and inflammation
Phthalates	Several hours	Food, personal care products, polyvinyl chloride (PVC), electronics, scented products	Mixed evidence linking prenatal phthalates to child growth patterns, BMI, and adiposity; possible effect modification by sex	Adipogenesis induction, changes in β-cell structure/number; hepatic steatosis; decreased glycogen storage; transactivation of PPARγ and PPARα pathways; oxidative stress
Organochlorine pesticides (e.g., DDT)	60 days up to 10–15 yr, depending on compound	Pesticides, food	Prenatal concentrations of DDT metabolites associated with increased body size in childhood and adulthood	Reduced insulin secretion; glucose intolerance; dyslipidemia
Perfluoroalkyl substances (PFASs)	Several years	Food, water-, and stain-repellent products, fire-fighting foams	Associations between prenatal exposure and higher cholesterol, BMI, adiposity (particularly in girls)	Dysregulation of lipid homeostasis; impaired glucose tolerance; hepatic stenosis; disrupted hepatocyte development; changes to gut microbiome

BMI, body mass index; DDT, dichlorodiphenyltrichloroethane; PPAR, peroxisome proliferator-activated receptor.

As with the majority of work on MDCs, epidemiological evidence is limited and tends to focus on crude outcome measures such as BMI and obesity in childhood. To date, two studies have linked higher prenatal BPA levels to higher BMI or greater adiposity. In a New York City cohort ($n = 375$), prenatal BPA concentrations were positively associated with FM at age 7 yr in girls but not boys (431). Similarly, in a Spanish study maternal BPA concentrations (in the 1st and 3rd trimesters) were positively associated with children's BMI and waist circumference *z* scores at age 4 yr, although no sex differences were noted (432). By contrast, three other studies have demonstrated inverse associations. In a study of Mexican American children ($n = 311$), there was an inverse relationship between maternal BPA levels during pregnancy and daughters' BMI and adiposity at age 9 yr but no associations observed in sons (433). In a European cohort ($n = 500$), first-trimester BPA concentrations were inversely associated with BMI *z* scores and adiposity in girls in early childhood, whereas the opposite relationship was observed in boys (434). However, in a Cincinnati, Ohio cohort ($n = 297$), higher BPA concentrations in the second and third trimesters were associated with nonsignificantly lower BMI in early childhood (435). Notably, two additional studies (one in boys only) indicated no discernible relationship between prenatal levels and children's body size at birth (436) or adiposity in middle childhood (437). Differences in the timing of prenatal urine sample collection and the type and timing of obesity-related outcomes measured may contribute to the seemingly inconsistent findings across studies, and the observations of sex-specific effects are consistent with the larger literature on the impacts of endocrine-disrupting chemicals.

Several human studies have also examined relevant metabolic biomarkers. In a German cohort, third-trimester BPA levels were associated with reduced promoter methylation and expression of mesoderm-specific transcript (MEST), a member of the α/β hydrolase fold superfamily believed to regulate early adipose tissue development and adipocyte size. Notably, cord blood *MEST* promoter methylation was observed to be a mediator of the relationship between maternal BPA concentrations during pregnancy and child BMI *z* scores (through age 6 yr), and additional work in animal models and in vitro further suggests an important role for *MEST* (438). Maternal first-trimester BPA concentrations have also been linked to reduced cord blood IGF-2 and PPARγ methylation in female infants (439). In a cross-sectional study in adults, urinary BPA was associated with higher β-cell activity, hyperinsulinemia, and insulin resistance, particularly in men, but there is a current

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paucity of analogous work on developmental exposures (440). Although much less studied, a host of related newer compounds frequently used as BPA substitutes in consumer products may be of interest given their close chemical similarities. In some studies, structural analogs such as bisphenol S (BPS) and bisphenol F (BPF) may share BPA's adipogenicity, causing lipid accumulation and expression of adipogenic markers in vitro (441, 442). As these compounds are increasingly used as BPA replacements, understanding their potential metabolic effects will be important.

In vitro studies offer the strongest evidence of potential mechanisms leading to BPA-induced metabolic disruption, and many have reported changes in adipogenesis following BPA administration, particularly in estrogen receptor (ER), glucocorticoid receptor (GR), insulin receptor, PPARγ, MAPK, and protein kinase B (Akt) pathways (441, 443–447). In human adipocyte stem cells exposed to 100 pM–10 μM/day of BPA, ER-mediated adipogenesis occurred and was blocked when an ER antagonist was added (446). Differentiation of 3T3-L1 preadipocytes is also stimulated by low, environmentally relevant doses (0.01–10 nM) of BPA, with resulting increases in expression of PPARγ and CCAAT-enhancer-binding protein (C/EBPα) (443, 448, 449). BPA-exposed 3T3-L1 preadipocytes also showed enhanced lipid storage, impaired glucose utilization, and greater expression of the inflammatory cytokines IL-6 and IFN-γ, suggesting metabolic dysfunction and inflammation (448, 450). Levels of fatty acid binding protein 2 (aP2), the terminal marker of adipogenesis, may be upregulated as well, through direct action on the Ap2 promoter (443). At maturity, BPA-exposed adipocytes show increases in lipid accumulation, reductions in insulin-stimulated glucose utilization, and increased mRNA expression of leptin, IL-6, and IFN-γ (448). Reductions in insulin-stimulated glucose uptake following BPA administration have also been observed in 3T3-F442A cell lines (451). BPA acts on the pancreas as well. Studies in mouse and human islet cell lines indicate that low-dose BPA enhances β-cell insulin production through ERα and ERβ pathways (452, 453). Oxidative stress pathways may be important to consider as well. For example, in INS-1 (pancreatic β) cells, BPA promotes oxidative stress, induces reactive oxygen species (ROS), and disrupts mitochondrial structure and gene expression, resulting in glutathione depletion and DNA damage (113, 454). Thus, the molecular mechanisms linking BPA exposure to metabolic dysfunction may be implicated in contributing to the increased prevalence of metabolic diseases in industrialized nations, independent of or in concert with maternal diet and health.

The in vitro work is complemented by a large experimental rodent literature on BPA as a metabolic disruptor, much of it focused on body size outcomes, but results of these studies are often conflicting. For example, whereas some studies have observed that developmental exposure to BPA is positively associated with offspring body weight (455–458), others have noted inverse (459, 460) or no (461, 462) associations. What appear to be disparate findings may actually represent methodological differences in terms of the animal models used; doses, routes, and timing of BPA administration; postnatal diets; and offspring sex and age at outcome assessment rather than a lack of reproducibility (463, 464). Noting great heterogeneity, a recent meta-analysis of >60 experimental rodent studies recently concluded that developmental BPA exposure was positively associated with FM, triglyceride levels, and free fatty acid levels but negatively associated with overall body weight (464). Relationships differed by sex, moreover, with developmental BPA exposure linked to increased triglycerides and free fatty acids in males but inversely associated with body weight and leptin in females.

As supported by in vitro evidence, BPA may impact body size and metabolic markers in rodents by acting on adipose, pancreatic, and/or hepatic tissue. In male (but not female) mice, for example, BPA exposure in utero caused hypomethylation of the promoter for the body weight-linked *fggy* carbohydrate kinase gene in gonadal white adipose tissue, resulting in increased transcription as well as increased whole body weight and gonadal fat weight (465). In the pancreas, after maternal BPA exposure juvenile female mice exhibited insulitis in the pancreatic islets, suggesting possible accelerated β-cell attrition through immune activation (466). Effects on the liver have been examined at length as well. At both high (200 mg) and low (20 mg) doses, in a rat model BPA reduced hepatic glucose oxidation and glycogen content, possibly via impaired insulin signal transduction (467). Hypermethylation of the hepatic glucokinase promoter has been observed along with the reduction in hepatic glycogen levels (468). Effects on the liver may be exacerbated by the postnatal environment. Prenatal BPA exposure paired with a high-fat diet induced a nonalcoholic steatohepatitis-like phenotype in male rodents including increased lipid levels in hepatocytes and liver inflammation; effects of BPA-exposed animals on low-fat diets were much more subtle and included moderate steatosis as well as changes in insulin signaling (469, 470). It is also possible that BPA treatment may indirectly impact fetal development through effects on maternal metabolic function during pregnancy. One study demonstrated long-lasting changes in maternal insulin secretion and sensitivity, increased β-cell apoptosis and reduced β-cell mass, and reduced expression of the cell cycle inhibitors p16 and p53 (471). Overall, developmental BPA exposure appears to alter the liver methylome, which may contribute to insulin

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resistance in adulthood through changes in nuclear receptor expression or mitochondrial dysfunction (472).

4.2.2. Phthalates.

Like BPA, phthalates are a class of chemicals widely used in plastics manufacture and are widely found in consumer goods such as food, personal care products, and vinyl products (e.g., flooring, upholstery) (473). Phthalates can leach from their constituent products, with human exposure occurring through inhalation or ingestion or dermally. Although they are readily metabolized in the human body and have a short half-life (several hours), because of ongoing, repeated environmental exposure most major phthalate metabolites are detectable in the urine of 90–100% of individuals sampled (474–477). Phthalates are also widely detected in placenta, cord blood, and amniotic fluid samples, indicating fetal exposure (478–480).

Of the many phthalates in mass production, di-(2-ethylhexyl)phthalate (DEHP) and its metabolite mono-(2-ethylhexyl)phthalate (MEHP) have attracted the most attention in the context of metabolic dysregulation and obesity. In juvenile animals, even a single dose of DEHP promotes adipogenic gene expression, including reduced *UCP1* expression indicating upregulation of white adipocyte differentiation (481). More prolonged in utero DEHP exposure in rodents is linked to a suite of metabolic changes including visceral fat accumulation and increases in circulating leptin, insulin, lipid, and glucose concentrations (187, 481, 482) These effects may be stronger in male offspring and compounded by a high-fat postnatal diet (483). In a recent meta-analysis of 31 rodent studies, developmental DEHP exposure was associated with significantly increased fat (pad) weight and nonsignificantly decreased body weight (464). Although fewer studies have examined metabolic end points after phthalate exposure, evidence suggests potentially sex-specific effects on the developing liver, pancreas, and muscle tissue. In female animals, gestational DEHP exposure led to hyperglycemia when insulin levels were reduced, along with disruptions in β-cell ultrastructure, lower β-cell mass, and lower islet insulin content (112, 484). In males, on the other hand, developmental DEHP exposure has been linked to increased insulin concentrations but normal glucose tolerance, and these sex-specific findings have been noted in some human work on phthalates and diabetes risk (484, 485). Developmental DEHP exposure can also lead to hepatic steatosis and decreased glycogen storage, which could plausibly occur through nuclear receptor changes for peroxisome proliferator-activated receptor (PPAR)α, chimeric antigen receptor (CAR), or pregnane X receptor (PXR) (397, 486–488). Moreover, such effects may be tissue specific, as the JAK/STAT pathway is upregulated in adipose tissue but downregulated in the liver after DEHP exposure in rats (489). Finally, changes in glycolytic intermediates in liver and muscle, suggestive of altered lactate and glucose handling, are evident after chronic DEHP exposure in adult rodents; however, analogous developmental work has not been conducted thus far (490).

A number of in vitro studies have documented transactivation in nuclear PPARγ and PPARα pathways by DEHP and/or MEHP (187, 491–494). Along with Runx2, PPARγ has been proposed as the "master regulator" of fat cell differentiation and is a requisite for normal adipocyte development. In fact, PPARγ-null mice lack adipose tissue, and in humans heterozygous loss-of-function mutations lead to lipodystrophy and insulin resistance (495–497). PPARγ plays a key role in regulating the expression of adiponectin, leptin, TNF, and resistin, ultimately having a profound impact on glucose homeostasis (496). In humans, maternal first-trimester urinary DEHP metabolite concentrations are inversely associated with methylation of PPARα as well as PPARα gene expression in cord blood (439). This work is complementary to rodent studies showing that maternal vitamin A supplementation reduced the expression of PPARα in offspring (97), emphasizing the confluence of dietary and environmental maternal exposures on offspring health.

As well, oxidative stress has also been examined in relation to phthalate exposure, such that in INS-1 cells DEHP administration resulted in oxidative stress as well as p53 and ATM activation, all of which may have been the result of dysregulation of lysosomal-mitochondrial pathways (498, 499). Human studies have also noted associations between urinary DEHP metabolite concentrations and oxidative stress biomarkers including 15-F2t isoprostane, 8-isoprostane, and 8-hydroxydeoxyguanosine (500, 501). The results of untargeted metabolomic analyses indicate dysregulation of multiple pathways, with MEHP exposure resulting in increased expression of genes involved in glyceroneogenesis, cytosolic phosphoenolpyruvate carboxykinase expression, and fatty acid release, suggesting fatty acid reesterification in human subcutaneous adipocytes (502). Finally, although the impact of metabolism-disrupting chemicals on muscle tissue has been understudied, work in L6 myotubes indicates that DEHP exposure downregulates GLUT4 (possibly through inhibitory chromatin modifications at the GLUT4 promoter), resulting in impaired glucose utilization (503, 504), and suggests a need for more attention to the role of muscle in this context.

Given the ubiquity of phthalate exposure in human populations and the compelling animal literature, there

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has been a great deal of interest in their impact on humans. In addition to several cross-sectional studies indicating that certain phthalate metabolites (including the DEHP metabolites as well as monobutyl phthalate and monoethyl phthalate) are positively associated with BMI and waist circumference in adults and children (505–508), several prospective pregnancy cohorts have now examined developmental phthalate exposures in relation to measures of childhood body size and adiposity. In a Spanish cohort ($n = 391$), maternal concentrations of the high-molecular-weight phthalate metabolites (averaged across the 1st and 3rd trimesters) were associated with slower growth from 0 to 6 mo and lower BMI z scores in boys but more rapid growth from 0 to 6 mo and higher BMI z scores in girls up to 7 yr of age (509). In a New York City cohort ($n = 330$), concentrations of non-DEHP metabolites in the third trimester were associated with lower BMI and FM, as well as smaller waist circumferences in boys, but not girls, at ages 5–7 yr (510). In Mexican Americans ($n = 345$), maternal diethyl phthalate (DEP), dibutyl phthalate (DBP), and DEHP metabolite concentrations (measured twice during pregnancy) were associated with increased odds of overweight/obesity in children at age 12 yr (511). No associations between late-pregnancy phthalate metabolite concentrations and childhood FM were observed in either sex in a second New York City cohort (512) or in a Cincinnati, Ohio cohort (513); however, sample sizes were notably smaller, $n = 180$ and $n = 219$, respectively.

4.2.3. Persistent organic pollutants.

In contrast to the short-lived BPA and phthalates, persistent organic pollutants (POPs) are contaminants that persist in the environment and bioaccumulate in living organisms because of their resistance to chemical, biological, and photolytic breakdown. Cross-sectional analyses using NHANES data suggest that serum concentrations of a number of POPs are associated with increased risks of type 2 diabetes, metabolic syndrome, and insulin resistance, although the possibility that these disorders alter metabolism and storage of POPs resulting in higher levels (i.e., reverse causation) cannot be ruled out (514–516). Perhaps the most notorious POP is dichlorodiphenyltrichloroethane (DDT), an organochlorine pesticide that was banned in 1975 in many countries but still persists in the environment and is used for malaria control in some regions of the world. Evidence of DDT's metabolism-disrupting effects is strong. In vitro, DDT reduces insulin secretion following stimulation with glucose or tolbutamide, suggesting diabetogenic effects (517). Similarly in rodents, a wide range of adverse outcomes (including glucose intolerance, hyperinsulinemia, dyslipidemia, and reduced energy expenditure) were observed in females after prenatal exposure to DDT followed by a high-fat diet (518). The obesogenic effects of DDT appear to be transgenerational, moreover, with obesity observed in rodents of the F_3 generation (which received no direct exposure) (519). Multiple epidemiological studies have consistently linked concentrations of the DDT metabolite dichlorodiphenyldichloroethylene (DDE) to body size across childhood (520–524), and in an older United States cohort prenatal DDE concentrations were associated with daughters' BMI in adulthood (525).

Given the long-standing bans on the use of DDT and other organochlorine pesticides in most parts of the world, other POPs in current production, such as perfluoroalkyl substances (PFASs), have emerged as potentially being of more urgent concern. In addition to numerous documented water supply contaminations in the United States (526, 527), leading sources of exposure to PFASs, including perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), include food, stain- and water-repellent household products (clothing, upholstery, cleaning products, polishes) and fire-fighting foams (528). PFASs have been linked to changes in estrogen, androgen, and thyroid activity and have been implicated in lipid dysregulation (529–531). In adolescents and adults, including pregnant women, PFOS and PFOA exposure is consistently associated with elevated cholesterol levels, increased fasting glucose levels, and β-cell function (532–536), indicating altered lipid homeostasis. This epidemiological evidence is supported by experimental literature indicating that high-dose exposure to PFOS and PFOA alters triglyceride and cholesterol levels in rodents (537). Evidence of their developmental effects is growing as well. In a rodent model, maternal PFOS exposure was associated with reduced body weight in offspring as well as with a prediabetic phenotype including elevated fasting insulin and leptin, impaired glucose tolerance, and hepatic steatosis (538, 539). The hepatic effects of PFOA and PFOS may occur through downregulation of hepatocyte nuclear factor 4α (HNF4α), a critical regulator of hepatocyte development (540). Notably, HNF4α mutations result in a form of diabetes (maturity-onset diabetes of the young type 1), suggesting that PFASs (and other MDCs) acting on HNF4α may impact hepatocyte and β-cell function (541).

As well, exposure to these chemicals appears to alter lipid metabolism as demonstrated in a cohort study in Boston in which maternal PFOS, PFOA, and perfluorodecanoic acid (PFDeA) concentrations were associated with higher cholesterol levels in girls in middle childhood, including both higher LDL and HDL concentrations (531), as well as reduced insulin resistance in girls in middle childhood (542). In the same cohort, maternal PFOA concentrations were also positively associated

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with BMI, dual X-ray absorptiometry (DXA) total FM, and skinfold thickness in girls but not boys (543). No associations were observed in male offspring or in relation to leptin or adiponectin levels. In a meta-analysis of 10 studies, prenatal PFOA concentrations were associated with increased risk of childhood overweight, higher childhood BMI, and an increased risk of childhood adiposity (544).

Above in this review, a brief discussion of the role of the microbiome on growth was presented, and the role of the microbiome in relationship to nutrient availability and the influence on health and disease risk is clear. Again, the intersection between human diets and environmental exposures is relevant in terms of metabolic diseases, as recent evidence suggests that PFOS exposure can alter the gut microbiome, perturbing gut metabolism in relation to arginine, proline, lysine, methane, and butanoate levels, and suggesting an additional route by which PFASs and other environmental chemical exposures may act as metabolic disruptors (545, 546). Therefore, future studies of environmental toxins and human health should be complemented with studies of the microbiome and other indicators of gastrointestinal health.

4.3. Considerations, Challenges, and Future Directions for Research on Environmental Exposures and DOHaD

The landscape of research on environmental exposures is constantly shifting as new chemicals emerge, production levels change, and policies are implemented. Moreover, there are a number of challenges and considerations that must be addressed to advance our understanding of how environmental chemical exposures may contribute to metabolic dysregulation and obesity. These include new advances in our understanding of how MDCs may impact physiology as well as methodological concerns that must be considered when designing future research.

4.3.1. Nonmonotonic effects.

MDCs provide compelling evidence that the toxicological tenet "the dose makes the poison" is not always true. Like hormones, MDCs can be physiologically active at extremely low levels. Endocrine activity depends not only on hormone concentrations but on other factors including receptor densities and isoforms, binding proteins, and transporters; characterizing the dose or exposure is not necessarily sufficient to predict the physiological response. Defining "thresholds" above which harm may occur is often impossible, and dose-response relationships are frequently nonmonotonic (401, 408). In a meta-analysis of the experimental animal literature on BPA, for example, associations between BPA exposure and relevant outcomes (body weight, triglycerides, and FFA) were stronger in studies with exposures below the reference dose compared with higher doses (464). Similar findings have been reported for phthalates, where low (0.05 mg/kg body wt/day), but not high (0.25–0.5 mg/kg body wt/day), doses of MEHP were associated with increased weight, FM, and altered lipid and glucose profiles in offspring (493). These unexpected relationships are important to keep in mind given that much of the experimental work on MDC exposure (particularly the early studies) dosed animals with MDCs at supranormal levels (547–549).

4.3.2. Epigenetic mechanisms.

As noted in earlier sections of this review, epigenetic modifications are clearly central to potential mechanisms in a number of metabolic diseases related to poor growth or placental development. Likewise, developmental sensitivity to MDCs may occur through epigenetic signaling mechanisms (e.g., DNA methylation, histone marks, noncoding RNA) (397). The classic example of this phenomenon comes from work by Dolinoy et al. (550), who demonstrated that when pregnant mice were fed genistein, the major phytoestrogen in soy, in heterozygous offspring there was increased methylation of six c-g sites upstream of the Agouti coat color gene. This epigenetic change, which persisted through adulthood, resulted in a change in coat color toward pseudoagouti as well as reduced susceptibility to obesity in adulthood (550). More recent work has begun to explore how MDCs may alter epigenetic signaling patterns over multiple generations, resulting in transgenerational transmission of metabolic risk.

Across multiple studies and laboratory groups, prenatal exposures to MDCs in the pregnant F_0 generation have been linked to obesity through at least the F_3 generation. Importantly, in this work, F_0 and F_1 animals are directly exposed to MDCs, the F_2 generation is exposed as germ cells, but the F_3 generation receives no direct chemical exposure (397). In a series of elegant studies, when pregnant mice were given environmentally relevant doses of tributyltin, an endocrine-disrupting biocide, effects on metabolism were evident into the F_4 generation, particularly in male offspring. Males showed a signature thrifty phenotype, gaining weight rapidly on high-fat diets and retaining that weight even when subsequently switched to a low-fat diet. Changes in chromatin structure, DNA methylation, and gene expression were noted in the F_4 generation as well (551). Parallel work on exposure to an MDC mixture containing BPA and phthalates (DEHP and DBP) demonstrated similar increases in

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obesity in the F_3 generation concomitant with reproductive disorders in both sexes (552). F_0 BPA exposure, similarly, results in glucose intolerance and insulin resistance two generations downstream and is accompanied by decreased hepatic glucokinase expression and hypermethylation of the relevant gene promoter (553). The majority of this literature has focused on changes in DNA methylation occurring after MDC exposure; however, there is a clear need for more research on other potential mechanisms (401). MDCs may effectively "reprogram" germ line cells and/or alter the activity of somatic cells that support their survival and differentiation (405). Epigenetic mechanisms also provide a plausible way by which paternal MDC exposures may be transmitted to offspring via sperm epimutations, thereby increasing obesity risk in offspring (554).

4.3.3. Timing of exposure.

In terms of precise timing of exposure and fetal outcomes, there may be differential fetal susceptibility to metabolic disruption depending on gestational age at exposure. At present, little is known about critical periods of gestation during which chemical exposures may "program" obesity, and most of the human literature has relied upon chemical exposures measured opportunistically. This presents a particularly acute issue in the case of chemicals like BPA and phthalates that have very short half-lives in the body (hours or days), resulting in considerable potential for exposure misclassification. For these chemicals, human observational studies really represent a "snapshot" rather than a comprehensive characterization of exposure during gestation. For persistent chemicals like PFASs, this is less of an issue, as a single measurement provides a reasonable estimate of exposure across the whole pregnancy.

The issue of the timing of exposure is compounded when we consider a "two-hit" model in which the effects of a prenatal exposure are unmasked or magnified when a second exposure during a subsequent critical period occurs. As an example, in female mice exposed to BPA in utero, dysregulation of triglyceride levels and glucose/insulin homeostasis is heightened in animals that experienced a second, peripubertal BPA exposure (463). Other studies have examined second hits in the form of high-fat diets (555, 556), suggesting that one way to look at MDCs is as altering developmental set points, which thereby increases sensitivity to subsequent metabolic dysregulation. Consistent with this model, some exposures like DDE appear to restrict growth in utero, akin to the classical thrifty phenotype, and it may be the subsequent rapid-catch up growth on a high-fat diet that drives metabolic dysregulation (522).

4.3.4. Sexually dimorphic effects.

As evidenced by the literature discussed, the effects of MDCs on obesity and metabolic function frequently differ by sex. This is not surprising given that in many cases the underlying hormone systems, as well as patterns of fat deposition and adipocyte endocrine function, are sexually dimorphic. Chemicals like BPA also have sex-specific effects on the developing brain and act on sexually dimorphic areas such as the hypothalamus, which may have important implications for feeding behavior and/or metabolic processes (557).

4.3.5. Outcome measurements.

Arguably the most relevant end points to assess metabolic dysregulation include diabetes diagnosis, insulin tolerance and resistance, β-cell function, and liver disease, all of which are most appropriately measured in adult populations. By necessity because the field is young and lacking sensitive biomarkers that are appropriate for study in children, the human literature on in utero MDC exposure in relation to early-life metabolic outcomes has focused on relatively crude measures of body size (such as BMI) or body composition. Moving forward, it will be important to adopt a life course perspective with longitudinal follow-up and assessment of relevant outcomes in prospective pregnancy cohorts later in life as well. This approach is needed, furthermore, to address "multiple hit" models in which the impact of prenatal exposures on metabolic function is only unmasked when paired with relevant postnatal exposures. Unfortunately, for the vast majority of environmental chemical exposures, laboratory analysis of banked biospecimens is the only way to accurately characterize early-life exposures. This stands in contrast to some other developmental exposures of interest (e.g., fetal growth, maternal smoking, and neighborhood stress) that may be captured through medical records, questionnaires, or administrative data sets. One notable exception is the innovative approach of measuring late gestational and early childhood exposures in deciduous teeth, and clearly additional methods to retrospectively quantify prenatal environmental chemical exposures are needed (558).

4.3.6. Confounding factors.

Identifying in utero exposures that impact metabolic function in humans presents a considerable challenge given the potential for confounding by factors including nonchemical stressors, infections, socioeconomic status, genetics, physical activity, and the microbiome. Diet may be a particularly important confounder given its

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important role in metabolic function and the fact that it is also a leading source of exposure to certain chemicals (like DEHP, BPA, and PFASs). Teasing apart prenatal and postnatal (and even preconception) exposures may be difficult as well, particularly for exposures that persist in the environment over long periods of time. There is also the very salient issue that although we tend to study chemical exposures individually, in reality, humans are exposed to a complex cocktail of environmental stressors that may have additive, multiplicative, or antagonistic impacts on physiology. Although there is great interest in better understanding how environmental chemicals interact with each other in mixtures and with other potentially modifying factors, improvement in biostatistical and modeling methods is needed to better estimate the impacts of ecologically relevant mixtures of exposures.

In summary, increasing evidence demonstrates that ubiquitous chemicals in the environment such as BPA, phthalates, and POPs can alter fetal physiological development to promote adiposity and metabolic disease in later life. Given the continuous development and production of new synthetic compounds, changing patterns of production among current-use chemicals, and the limited regulation of most synthetic chemicals, continued work on the health impacts of developmental exposure is essential.

5. SUMMARY AND CONCLUSIONS

There is now a substantial body of evidence supporting what was originally referred to as the "Barker hypothesis," and this review updates us on the main drivers predicting a poor in utero environment and long-term metabolic disease, such as exposomes including external stresses, poor maternal diet, and environmental contaminants, which have both direct and indirect effects on the developing fetus. What comes into greater focus in this review is the role of the placenta as both a thermostat of internal insults to the fetus and a direct regulator of fetal growth—with or without compromise. Moreover, this review illustrates both the challenges and opportunities posed by the postnatal environment. Collectively, the animal studies would suggest that regardless of the origin of fetal growth restriction, there is no question that the extent of growth in postpartum life will exacerbate the dysmetabolism present. The discrepancies in the clinical studies arise from variations in the methods used to identify and measure fetal growth restriction versus postnatal metabolic measurements. With the onset of metabolomics and early imaging of both the placenta and fetus, the DOHaD field will be strengthened to better predict fetal growth restriction and ameliorate the incidence of noncommunicable diseases as we enter the next decade. In addition, advances that better manage IUGR infants in postpartum life will undoubtedly further reduce the severity of dysmetabolism in a world population that continues to be exposed to malnutrition, inactivity, and pollution.

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AUTHOR CONTRIBUTIONS

D.J.H., T.L.P., and D.B.H. prepared figures; D.J.H., T.L.P., E.S.B., and D.B.H. drafted manuscript; D.J.H., T.L.P., E.S.B., and D.B.H. approved final version of manuscript.

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