Review

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Asher Ornoy *, Boniface Echefu, Maria Becker

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Review

Prenatal Origin of Childhood Overweight, Obesity and Insulin Resistance, with Special Emphasis on Maternal Diabetes, Excessive Weight, Nutrition and Hormone Imbalances

Asher Ornoy [1,2,3,]*, Boniface Echefu [1] and Maria Becker [1]

[1] Department of Morphological Sciences and Teratology, Adelson School of Medicine, Ariel University, Ariel 40700, Israel
[2] Hebrew University Hadassah Medical School, Jerusalem 9112102, Israel
[3] Jerusalem Multidisciplinary College Jerusalem, Israel
* Correspondence: ornoy@cc.huji.ac.il

Abstract

Overweight at childhood, adolescence and adulthood is now considered a world-wide epidemic. A variety of preventive and therapeutic measures are being developed with partial success. Since the pioneering studies of D.J. Barker linking maternal famine in pregnancy to long-term undesirable effects on the offspring, the "metabolic syndrome", that stems from long-lasting epigenetic changes, it became evident that there are many undesirable events which affect in utero fetal growth and development and persist postnatally, through childhood and adulthood. The purpose of this review is to discuss the prenatal factors that may have long term effects on postnatal weight gain and obesity that are major contributors to this epidemic of "overweight and obesity". Understanding these factors might help us find more effective preventive measures. The list of these prenatal undesired factors is connected to some maternal diseases that affect fetal growth: pregestational and gestational diabetes, p-pregnancy maternal overweight and obesity, excessive weight gain in pregnancy, placental dysfunction and maternal hormonal imbalances in pregnancy. They all affect fetal growth often causing excessive fetal growth (macrosomia) and sometimes diminished growth (small for gestational age). Due to long lasting epigenetic changes, they often lead to insulin resistance that induces metabolic alterations which may lead to increase in food intake, overweight and obesity. Studies also demonstrate that increased exposure in pregnancy to some teratogens, like endocrine disruptors and cigarette smoking may affect fetal growth and adiposity, inducing epigenetic changes which lead to postnatal insulin resistance, overweight and obesity. Normalization of intrauterine fetal growth might open a new area of preventive measures for childhood obesity that might be more effective than the currently used dietary measures. In addition, early diagnosis of insulin resistance and proper treatment in addition to diet and exercises may be a more effective approach.

Keywords: prenatal origin; maternal overweight; childhood obesity; insulin resistance; metabolic syndrome; diabetes; epigenetic effects

1. Introduction

Prenatal and postnatal growth are influenced by genetic and environmental factors. Among the non-genetic environmental factors affecting the developing embryo and fetus are maternal over or under nutrition, maternal obesity, excessive gestational weight gain and related metabolic and environmental disturbances. They are often linked to fetal overgrowth and increased postnatal adiposity [1–5]. Disturbed placental function is an additional important factor [2,3]. These changes in intrauterine growth patterns may subside after birth but often have a major effect on postnatal growth, increasing weight gain and adiposity. Moreover, even infants with reduced growth in utero may often become overweight after birth [2]. Well-studied examples are maternal diabetes in pregnancy that induce in humans and in experimental animals a variety of epigenetic changes with long-term effects on postnatal growth and health at childhood and adulthood [6–8].

Only about 80% of newborn infants have birth weight in the normal range, as about 10% are born small for gestational age (SGA) and 5-10% have excessive weight at birth (macrosomic) [9]. SGA and macrosomia may be associated with preterm or post term delivery [10,11], congenital anomalies and neurodevelopmental alterations and often have long-term neurodevelopmental consequences [6,11–13]. Asher will add and often have ling erm neurodevelopmental consequences. Abnormal fetal growth may also induce insulin resistance, type II diabetes, obesity, dyslipidemia, hypertension, and cardiovascular diseases at childhood, adolescence and adulthood [6,14,15]. Finally, maternal exposure to teratogens (i.e., maternal infections (cytomegalovirus or other teratogenic infectious agents), maternal alcohol abuse, heavy smoking may affect intrauterine growth that also persists postnatally [3,16].

According to the developmental origins of health and disease hypothesis [17] inadequate nutrient availability during fetal life induces epigenetic changes that support adaptive metabolic programming, commonly referred to as the “thrifty phenotype” [18]. This adaptive response enhances energy efficiency and prioritizes survival under conditions of intrauterine scarcity. However, when individuals exposed to such fetal undernutrition encounter an energy rich postnatal environment, this metabolic programming may become maladaptive, increasing the risk of obesity, insulin resistance, and cardiometabolic disease later in life. [18].

Some of the prenatal causes influencing postnatal weight and health are well delineated and will be discussed in this review, especially the role of maternal nutrition, environmental agents such as exposure to endocrine disruptors, heavy smoking and the role of hormones, especially leptin, insulin and growth hormone [2,18–20]. Many prenatally originating effects are epigenetic changes, inducing long-term changes in the expression of different genes related to energy metabolism and/or to growth factors. Finally, insulin resistance seems to be a very important contributor to different health complications related to the long-term effects of negative changes in prenatal metabolic development. The crucial and dominant role of epigenetic changes in these processes will be delineated

2. Maternal Diseases Affecting Prenatal Growth Causing Postnatal Overweight

2.1. Maternal Diabetes in Pregnancy

Pregestational diabetes Mellitus (PGDM) may be associated with an increased rate of spontaneous abortions, intrauterine death and congenital malformations among the offspring [15]. Gestational Diabetes Mellitus (GDM) does not seem to increase the rate of congenital malformations in the offspring but might affect fetal growth and be associated with a higher rate of health problems later in life, including overweight and obesity or neurobehavioral problems which may start at childhood. The prevalence of these complications is reduced by optimal glycemic control. Offspring of diabetic mothers may be macrosomic, SGA or of normal birth weight, depending on the severity of diabetes, presence or absence of complications and the degree of diabetic control [6,15].

Maternal hyperglycemia increases transplacental glucose delivery, stimulates fetal pancreatic insulin secretion leading to enhanced lipogenesis, glycogen storage, and somatic growth [15,21]. Fetal hyperinsulinemia results in over-growth, whereas fetal insulin-deficiency is associated with intrauterine growth retardation (IUGR) [22,23]. Optimal control would normalize fetal growth while poorly controlled diabetes or diabetic complications: (i.e., diabetic nephropathy) often result in small or large-for-gestational age infants [24,25].

Several studies have examined the maternal Insulin Growth Factor 1 (IGF-I) and insulin growth factor binding protein 1 (IGF1BP) system in pregnancies complicated by diabetes. In diabetic pregnancies, maternal circulating IGF-I levels are generally reduced, whereas fetal IGF-I concentrations are increased in infants born to mothers with type 1 (T1DM) and type 2 (T2DM) diabetes compared with non-diabetic controls [26,27]. Elevated IGFBP-3 levels have also been reported in both maternal and fetal serum in T1DM pregnancies [28]. Disruption of the placental growth hormone (PGH)–IGF-I–IGFBP-3 axis in T1DM pregnancies may alter normal fetal growth regulation and contribute to fetal overgrowth and macrosomia [28].

Gillman et al. found among 14,881 children at the age of 9–14 years that 465 children were born to mothers who were diabetic in pregnancy (PGDM or GDM) [29]. Of these children, 9.7% were overweight at early adolescence, while only 6.6% of children born to mothers without GDM were overweight. A higher birth weight independent of maternal GDM, and maternal GDM, were predictors of increased body weight at adolescence. In addition, maternal BMI (kg/square meter) was a high predictor of children's weight. In adolescents born to mothers with GDM, the BMI was 26.0, as opposed to only 20.9 in controls. Moreover, children of mothers with GDM that were LGA, but not LGA infants born to non- diabetic mothers, were of high risk to develop at 6-11 years the "Metabolic Syndrome" with insulin resistance [30].

We examined 5-12 years old children born to mothers that developed GDM and children born to mothers with well controlled PGDM, at ages 5.2–12.2 years in comparison to children born to healthy control mothers [31,32]. While we found no difference in cognitive ability, head circumference or height between the children of diabetic mothers and controls, a significant increase in body weight and BMI in the children born to diabetic mothers was observed. The differences were more pronounced in the elder children aged 9-12 (preadolescence) compared to the younger, 5-8 years old children. Philipps et al. in their metanalysis found higher BMI z-scores in infants of PGDM and GDM mothers [33]. However, when adjusted for maternal pre-pregnancy BMI, the differences subsided. Similarly, Logan et al. [34] assessed the adiposity of 24,000 children of diabetic mothers from 35 studies. The increase in adiposity was most prominent in infants of T1DM mothers and less in offspring of GDM mothers. They, too, found that after adjusting to maternal, adiposity the differences became insignificant. Similarly, Hammoud et al. [35] reported that macrosomic children of diabetic mothers were at higher risk to develop overweight than children born AGA. The highest differences were at preadolescence and early adolescence. There were no differences in height among the groups. Several other, more recent studies reached similar conclusions [34,35].

Deng et al., studied in 506 mother-child pairs the association between maternal fasting plasma glucose levels or after an oral glucose tolerance test on the weight of the offspring at 18 years [36]. They found a direct correlation between maternal plasma glucose levels and the adiposity of the offspring. This tendency was more prominent in children born to mothers with GDM.

In summary: infants of diabetic mothers, especially those born macrosomic, have a high susceptibility to become overweight at preadolescence and adolescence.

2.2. The Effects of Maternal Overweight in Pregnancy on Growth During Childhood

Maternal obesity is frequently accompanied by hyperinsulinemia and increased insulin resistance, expanded pancreatic beta-cell mass, and higher insulin secretion, further stimulating placental nutrient transport interacting with the insulin growth factor (IGF) signaling pathway to promote fetal tissue growth [37]. Various studies support the importance of the placental growth factor (PGH) and IGF axis in determining fetal growth outcomes. Maternal plasma PGH levels were positively associated with gestational age and fetal growth [38,39].

There is a direct relationship between maternal obesity and fetal and postnatal growth [40–44]. Excessive gestational weight has been linked to a higher risk of adverse pregnancy outcomes, including hypertensive disorder of pregnancy, gestational diabetes, cesarean delivery, preterm birth, and the delivery of macrosomic infants [44]. Moreover, these macrosomic infants tended to develop at adulthood type 2 diabetes, hypertension and a higher mortality rate from coronary artery disease compared to normal -weight newborns of obese mothers. In addition, a high maternal pre-pregnancy body mass index (BMI) increased the risk of preeclampsia [45] and of developing gestational diabetes [46]. Khashan et al. carried out a population register-based cohort study from the North Western Perinatal survey (n=99,403 babies born during 2004–2006) and found that overweight and obese women have a higher risk of macrosomia and Caesarean delivery and a lower risk of preterm delivery [42]. The relative risk of macrosomia in relation to overweight, obesity and morbid obesity was increased by 1.7, 2.7 and 4.8, respectively.

Offspring of overweight women are of high risk to develop at adolescence overweight and abdominal obesity-i.e., disproportionate accumulation of abdominal fat that predisposes to a higher risk of cardiovascular disease [47,48]. In a cohort of 4168 children from the longitudinal Northern Finland cohort of 1986, the rate of overweight in the offspring of mothers who had both GDM and pre-pregnancy overweight was 40% (OR of 4.05) and abdominal obesity was observes in 25.7%. In non-diabetic obese women, it was reduced to 27.9% and 19.5%, respectively [48].

In the EPOCH cohort, 46% of 312 children were exposed to prenatal overnutrition. Although BMI z-scores were similar at age 10, exposed children showed 14% higher fasting insulin. Elevated insulin at 10 years strongly predicted greater adolescent adiposity, alongside higher fasting glucose by age 16. By adolescence, 13.9% of exposed youth developed overweight/obesity versus only 5.4% of unexposed peers. These findings indicate that prenatal overnutrition induces early hyperinsulinemia, promoting subsequent adiposity, insulin resistance, and emerging dysglycemia, supporting an insulin-hypersecretion pathway to metabolic risk [49].

Several studies also found an association of maternal obesity with a higher risk of fetal growth restriction [50–52]. A prospective study of 912 mothers [52] , examined how the woman's BMI before pregnancy affected her child's birth weight. Overall, 6.6% of infants were LBW, 2.3% had FGR, and 10.6% were macrosomic. Low birth weight infants were seen only among women whose gestational weight gain was within the recommended range.

2.3. Excessive Weight Gain in Pregnancy and Postnatal Growth:

The optimal increase in maternal weight during pregnancy is largely dependent on the maternal BMI before pregnancy. The American Society of Obstetrics and Gynecology recommends optimal weight gain in relation to pre-pregnancy BMI: For underweight, low BMI women, 12.7-18.1 Kg, for women with normal body weight 11.3-15.9 Kg and for overweight and obese women (BMI over 30) it should be no more than 6.8-11.3 Kg [53]. Accordingly, pregnant women in any of these categories who gain more weight may endanger themselves and their children.

Baran et al. studied the pregnancy outcome in 749 mothers and children measuring the weight and height of 4-15 years old boys and girls in relation to maternal weight gain during pregnancy [54]. They found that mothers of children that were overweight/obese at the time of study gained more weight during pregnancy compared to the mothers of children that had normal weight. Maternal age at delivery did not affect child's weight [54].

Perng et al., [55] reported the findings of a prospective study carried out in 1,090 mother-child pairs in "Project Vivo". They evaluated the possible associations between either a maternal gestational weight gain (GWG) or pre-pregnancy body mass index (ppBMI) and offspring adiposity, including inflammatory/metabolic biomarkers in mid-childhood (6–10 years). Positive associations of GWG and ppBMI with offspring overall adiposity was found. Moreover, higher maternal ppBMI was directly related to higher offspring leptin, high sensitivity C-reactive protein (hsCRP), IL-6, high systolic blood pressure (BP) and low adiponectin [55] whereas, GWG was associated with leptin levels. Similarly, Fraser et al. also reported the association of greater maternal pre-pregnancy weight and GWG up to 36 weeks of gestation with offspring adiposity and adverse cardiovascular risk factors [56]. Large-scale pooled evidence with long follow-up, reported by Voerman et al. analyzed multiple cohorts and also found that higher maternal pre-pregnancy BMI and gestational weight gain were associated with increased risk of childhood overweight/obesity, often strengthening at later ages [57].

In summary: there are plenty of data showing that both pre-pregnancy high BMI and high weight gain in pregnancy are associated with long-term increase of postnatal weight and induce several important metabolic and endocrine changes in the offspring.

3. Insulin Resistance as a Major Mechanism of the Long-Term Effects of Maternal Diabetes, Overweight or Underweight on Offspring Adiposity

Several hypotheses try to explain the range of effects seen in offspring of diabetic or overweight mothers; the more important mechanism seems to be insulin resistance. Other possible mechanisms are the "*Thrifty genes or "Barker" hypothesis (metabolic syndrome)* via *epigenetic* changes, changes in leptin secretion, leptin insensitivity and hypothalamic programming.

The Role of Insulin and Insulin Resistance

Fetal insulin is one of the most important anabolic hormones regulating intrauterine growth. [7,58,59]. Maternal insulin does not cross the placenta; therefore, fetal insulin secretion is directly driven by maternal glucose availability [60–62]. Partial maternal insulin resistance develops in pregnancy from the end of the first trimester as a physiological adaptation evoked by placental hormones and maternal adipokines [63,64]. Satoru et al. found, in a longitudinal study of 137 low-risk mid and late-term pregnancies that maternal insulin resistance is associated with increased fetal fat deposition [65].

Insulin resistance syndrome seems to be the fundamental underlying problem in the pathogenesis of the "metabolic syndrome" (syndrome X) [66]. This term refers to the constellation of obesity, hyperglycemia, hyperlipidemia, and hypertension that cluster together to a syndrome with possible severe health consequences [66]. The maternal and fetal nutritional imbalance during pregnancy induces over-secretion of insulin that may cause in the fetus insulin resistance. Insulin resistance causes insulin over-secretion followed by insulin deficiency [67–69]. This seems to be a very important etiological factor in the later development of type 2 diabetes and cardiovascular disease.

In pregnant women with diabetes (PGDM or GDM), hyperglycemia induces fetal hyperinsulinemia. Elevated fetal insulin, which is an important mediator of the hypothalamic circuits, may affect its hypothalamic development [65,66,68–73]. Insulin in the brain decreases food intake while insulin depletion (or resistance) may promote hyperphagia. Singh et al. found a decrease in Neuropeptide Y (NPY), a protein that increases the thrive for food intake) in rat fetal hypothalamus when the dams were made diabetic by streptozotocin injection [73]. Fetal intra-cerebral injection of insulin with normal blood glucose levels caused a decline of the NPY protein suggesting that insulin directly reduces NPY levels in the brain and as a result reduces food intake. Insulin resistance may, therefore, increase food intake.

Gestational undernutrition, typically expressed as fetal growth restriction (SGA), follows a parallel, yet distinct pathway toward insulin resistance. Long-term follow-up of SGA infants reveals increased adiposity and insulin resistance, particularly when rapid catch-up growth occurs, aligning with the thrifty phenotype model wherein metabolic adaptations to scarcity become maladaptive in postnatal abundance [2,6,74]. Foundational DOHaD research similarly demonstrated that lower birth weight predicts adult insulin resistance and metabolic-syndrome features independent of adult BMI, affirming long-term consequences of early nutrient deprivation [18,75]. Clinical analyses further confirm that both undernutrition and overnutrition increased risk of later metabolic disorders, producing a U-shaped association between gestational nutrition and lifelong insulin resistance [76].

Together, these findings show that opposite forms of gestational malnutrition ultimately converge on the same metabolic trajectory: programmed insulin resistance emerging in childhood and worsening through adolescence. Nutrient excess drives this pathway via fetal hyperinsulinemia, enhanced adipogenesis, and early adiposity rebound, whereas nutrient deprivation triggers the classic thrifty phenotype-reduced fetal growth, impaired glucose oxidation, and lower insulin secretion-reflecting a conservative metabolic adaptation to constraint [6]. These converging observations reinforce the mismatch model of fetal metabolic syndrome, demonstrating how metabolic adaptations shaped by either constraint or excess become maladaptive when postnatal conditions diverge from fetal expectations, ultimately yielding a unified, developmentally programmed insulin-resistant phenotype [6,18,30,34].

It can be concluded that insulin plays a major role in the metabolism of many organs. Hence, insulin depletion resulting from insulin resistance may affect various organs, as summarized in Table 1:

Table 1. Possible undesired effects of insulin resistance on different organs:.

Organ affected	**The possible damage**
Brain (hypothalamus)	Reduced NPY, hyperphagia, obesity
Cardiac and respiratory system	Decreased function, heart failure
Vascular system	Hypertension
Adipose tissue	Hyperlipidemia, increased fat storage
Liver	hyperglycemia
Pancreas	Impaired beta cells regeneration and function
Skeletal system	Increase osteocalcin, impaired glucose homeostasis

Finally, insulin resistance often results from epigenetic changes induced by a variety of nutritional imbalances during pregnancy as described by us in section 5 of this review.

In summary: Due to the crucial role of insulin in many metabolic pathways and in different organs, insulin resistance leading to insulin depletion, seems to be the most important mechanism underlying the development of overweight and obesity. In addition, it may cause significant damage to many organs inducing hyperlipidemia, hypertension, diabetes and cardiovascular disease.

4. The Role of Hormones in Fetal Growth and the Effects on Postnatal Weight

Multiple endocrine and metabolic adaptations take place during pregnancy to secure sufficient energy, hormones and nutrient supply to the fetus [77,78]. Adipokines, particularly leptin and adiponectin, are key clinical biomarkers of maternal metabolic adaptation in pregnancy and are linked to fetal growth and early postnatal body composition. The following hormones secreted during pregnancy may have long-term effects on prenatal and postnatal growth.

4.1. Leptin

Maternal leptin concentrations in pregnancy increase in proportion to maternal adiposity and reflect the degree of pregnancy-associated insulin resistance. Elevated leptin levels in early pregnancy have been shown to predict the subsequent development of GDM [79], and correlate strongly with maternal anthropometric measures and fat mass [80].

During pregnancy, leptin is produced by maternal adipose tissue and by the placenta, particularly by syncytiotrophoblastic cells [81–83]. Leptin levels, especially hyperleptinemia, and leptin resistance, contribute to changes in energy balance during pregnancy and are associated with excessive gestational weight gain [84–86].

The maternal plasma leptin levels increase progressively throughout pregnancy, peak at term and subsequently decline to near pre-pregnancy levels around the time of delivery [87]. These increased levels of leptin reflect the increasing energy consuming processes of the maternal-placental-fetal unit [77,82]. An association between maternal leptinemia with pre-gestational BMI and maternal weight at the end of pregnancy was found [88].

The fetus appears to regulate its leptin independently, even in the context of maternal obesity. Moreover, fetal leptin levels, but not maternal, were found to be associated with macrosomic infants

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and with fetal insulin [89–92]. Higher leptin, C peptide and insulin levels were found in cord blood of macrosomic infants compared to controls [91,93–95] and were independent of maternal levels [96]. Tamai et al. demonstrated that higher cord plasma concentrations of leptin and IGF-1 were significantly associated with greater fetal adiposity, suggesting that these hormones may function as early biomarkers of increased fetal fat deposition and subsequent metabolic risk [91]. However, children with congenital leptin gene mutations or leptin receptor gene mutations generally have normal weight at birth [97,98].

Prospective human cohort studies have consistently linked cord blood leptin concentrations with postnatal growth [99,100], adiposity[100], neurodevelopment [101], and later cardiometabolic risk [102,103]. Deviations in leptin levels from an optimal range during critical periods of brain development may disrupt neurodevelopmental processes regulated by leptin, such as neuronal growth, synaptogenesis, and metabolic signaling inducing various neurodevelopmental deviations [104,105].

4.2. Adiponectin

In contrast to leptin, adiponectin, is inversely related to leptin blood concentrations and is reduced in obese people [106]. Generally, Adiponectin, a 30 kDa protein composed of 248 amino acids is exclusively produced by adipose tissue [107]. Maternal blood adiponectin levels decrease progressively during pregnancy, particularly in the third trimester. This decline is closely associated with increased maternal fat mass and reduced insulin sensitivity. A low first-trimester adiponectin is associated with increased insulin resistance and higher risk of GDM [108–110].

Clinical studies indicate that maternal adiponectin concentrations are associated with fetal growth and size at birth. Lower early mid-pregnancy adiponectin was inversely related to infant birth weight and increased the likelihood of delivering a macrosomic infant [111]. Fetal adiponectin levels are linked to postnatal growth patterns [99,112], body composition [99], and later-life cardiometabolic [113] and neurodevelopmental outcomes [114,115].

Mantzoros et al. reported in Project Viva that cord adiponectin was positively related to birth weight but inversely related to weight gain in the first 6 months, and predicted greater central adiposity by age 3 [99].

Buck et al. showed that lower adiponectin concentrations were associated with greater gains in BMI z-score from age 4 weeks to age 8 years while higher leptin concentrations were associated with higher BMI z-scores during the first 8 years of life [116]. Leptin and adiponectin concentrations, as well as the adiponectin-to-leptin ratio measured at 12 years of age, were strongly associated with adolescent adiposity and cardiometabolic risk. However, these associations were independent of leptin and adiponectin levels measured at birth [113]. These findings indicate that leptin and adiponectin during adolescence are more predictive of cardiometabolic risk than the hormone levels at birth.

Higher cord adiponectin levels were found to be associated with better cognitive outcomes, including working memory in childhood [115]. Cord adiponectin levels may be inversely associated with the risk of ASD [114].

4.3. Human Placental Hormones -Insulin Growth Factors (IGF) Axis, Fetal and Postnatal Growth:

IGF-1 is a polypeptide hormone structurally related to insulin, whose biological activity is regulated by several insulin-like growth factors binding proteins (IGFBPs). During normal pregnancy, the regulation of the maternal growth hormone-insulin-like growth factor (GH-IGF) axis undergoes a physiological shift [37,38,117]. As pregnancy progresses, the placenta increasingly contributes to endocrine regulation by continuously secreting placental growth hormone (PGH) into maternal circulation. From around 15-20 weeks of gestation (mid-term pregnancy), PGH progressively replaces pituitary GH in the maternal bloodstream and becomes the predominant circulating GH form until delivery, while pituitary GH levels decline to near undetectable concentrations [37,118]. Through this transition, PGH becomes the primary regulator of the maternal

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GH-IGF axis, stimulating hepatic production of maternal IGF-1, and subsequent gluconeogenesis, lipolysis, and anabolism in maternal tissues, increasing nutrient availability for fetal growth [119,120]. Therefore, PGH promotes maternal insulin resistance, enhances lipolysis, and increases circulating glucose and lipid availability, facilitating placental nutrient transfer to the fetus.

Several studies have shown that maternal obesity is associated with elevated circulating IGF-1 concentrations and low IGF binding protein profiles, which increase the bioavailability of IGFs and enhance fetal growth signals [121,122]. In addition, maternal obesity is frequently accompanied by hyperinsulinemia and increased insulin resistance, expanded pancreatic beta-cell mass, and higher insulin secretion, further stimulating placental nutrient transport interacting with the IGF signaling pathway to promote fetal tissue growth [37]. Clinical studies support the importance of the PGH–IGF axis in determining fetal growth outcomes, especially in the second and third trimesters of pregnancy [38,39].

The IGF system plays a central role in regulating fetal and early postnatal growth. Alterations in placental insulin–IGF signaling pathways have been proposed as one mechanism linking maternal obesity with an increased risk of obesity and other metabolic disorders in offspring [123]. IGF-1 concentrations measured in infants at 9 months of age are negatively associated with maternal obesity [124]. Overall, accumulating evidence suggests that intrauterine exposure to altered IGF signaling may shape early postnatal growth trajectories and contribute to the developmental programming of obesity and metabolic disease in the offspring.

In summary: Restricted and excessive fetal growth may represent different manifestations of disturbed developmental programming. These may arise from disturbances in the fetal endocrine environment, particularly within the IGF–insulin–leptin–adiponectin–ghrelin signaling network. These mechanisms highlight how the intrauterine environment can shape postnatal growth trajectories and influence susceptibility to metabolic and neurodevelopmental disorders in adolescence and adulthood.

5. In Utero Epigenetic Changes as a Mechanism Affecting Postnatal Weight Gain

5.1. Prenatal Nutritional Imbalance

Metabolic and nutritional factors may alter placental nutrient signaling and elevate fetal insulin, contributing to macrosomia, in line with the developmental origins of metabolic disease framework [125], consistent with Barker's hypothesis [126,127]. Increasing evidence now points to epigenetic programming as a central mechanism through which such maternal factors shape fetal metabolic trajectory, suggesting that environmentally induced alterations in DNA methylation and chromatin regulation during gestation may predispose infants to macrosomia and early-life overweight.

Periconceptional exposure to the Dutch Hunger Winter famine (1944–45) induced persistent hypomethylation at the IGF2 differential methylation region (DMR), detectable decades later in adult blood, as shown by Heijmans et al., with ~5% lower methylation ($P<0.05$) in exposed individuals versus unexposed siblings, restricted to early gestation ($P\_interaction=4.7\times10^{-3}$) [128], as confirmed by Tobi et al., with small but consistent changes (<3%; $P\_BH<0.05$) that were additive to IGF2 SNPs like rs2239681, without H19 DMR effects [129]. In contrast, early-life exposure to the Chinese Famine (1959–61) yields IGF2 hypermethylation in late adulthood, linked to higher cholesterol in the GRECF cohort [130]. This bidirectional patterning (hypomethylation in Dutch periconceptional cases versus hypermethylation in Chinese survivors) underscores famine timing, context, and population genetics as key determinants of developmental plasticity. These therefore establish prenatal undernutrition as a locus-specific epigenetic inducer that programs divergent cardiometabolic vulnerabilities consistent with thrifty phenotype theory. It is important to note that both, SGA and macrosomic newborns, both decreased and excessive fetal growth, are linked to similar later pathological changes: obesity, type 2 diabetes, and cardiovascular disease through metabolic imprinting adaptations initiated in utero [6].

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Excessive gestational weight gain (EGWG), even in women with normal pre-pregnancy BMI, is associated not only with increased weight at childhood but also with distinct maternal DNA methylation signatures that relate to fetal and neonatal body composition. In the Araraquara Cohort Study, 46 differentially methylated positions (DMPs) and 11 DMRs spanning 13 genes (including CPT1B, EMILIN1, and HOXA5) were identified in mothers with EGWG (>16 kg) compared to adequate GWG, with enrichment in insulin-resistance and hyperglycemia pathways. These methylation differences were significantly associated with fetal subcutaneous arm and thigh tissue. These findings support a potential role of the maternal methylome in the epigenetic programming of offspring adiposity [131].

5.2. Endocrine Disruptors, Fetal and Postnatal Growth and Epigenetic Changes

Lv et al. conducted a prospective birth cohort study of 285 mother–child pairs, integrating trimester-specific endocrine-disrupting chemical (EDC) exposure with cord-blood epigenome-wide DNA methylation profiling to assess early metabolic programming [132]. First-trimester exposure to, 2-Hydroxy-4-methoxybenzophenone (BP-3), Bis (4-hydroxyphenyl) sulfone (BPS), mono-ethyl phthalate (MEP), and triclosan showed the strongest associations with higher BMI z-scores in the offspring measured at two years of age, indicating susceptibility during the intrauterine developmental period. Mediation models revealed CpGs (in DUXA, TMEM132C, SEC13, ID4, GRM4, C2CD2, TSPAN6, and DNAH10 annotated positions) that accounted for 25–40% of the exposure–BMI relationship. These results demonstrate that prenatal chemical exposure may induce locus-specific methylation shifts detectable at birth, functioning as intermediaries between the intrauterine environment and accelerated adiposity by two years of age [132].

Agay-Shay et al. examined prenatal endocrine-disrupting chemical exposures in the Spanish INMA cohort using a multi-pollutant design, analyzing 27 biomarkers measured in maternal urine, serum, cord blood, and colostrum [133]. Among 470 children followed to 7 years of age, the authors used single-pollutant models and principal-component analysis to determine exposure signatures associated with growth. Persistent organochlorines-including HCB, β-HCH, PCB-138, PCB-180, and DDE-showed consistent dose-related associations with increased BMI z-scores and overweight risk at age seven, with the organochlorine factor (tertile 3 vs. 1) nearly tripling overweight risk (RR=2.59). In contrast, other pollutant groups, including BPA, metals, PBDEs, and most phthalates, showed null or inverse associations. Although this study did not assess DNA methylation directly, it points toward in-utero disruption of metabolic pathways, potentially via epigenetic mechanisms observed in other cohorts, linking organochlorine exposure to childhood overweight phenotypes[133].

Yang et al. analyzed third-trimester urinary polycyclic aromatic hydrocarbons (PAH) metabolites in 5600 mother–child pairs and found strong positive associations between prenatal exposure, particularly 3-hydroxyfluorene, 9-hydroxyphenanthrene, and 2-hydroxynaphthalene, and increased weight and higher odds of overweight at ages 4-6 [134]. Mixture analyses (g-comp, gWQS, BKMR) confirmed dose-dependent effects of combined OH-PAHs on child weight. Although the study did not assess molecular mediators, prior work shows that PAHs can induce in the fetus DNA methylation changes in genes regulating adipogenesis, insulin signaling, and oxidative-stress pathways, including altered methylation of CYP1A1, AHRR, and metabolic-relevant loci in cord blood and placenta. These epigenetic disturbances have been implicated in disrupted energy homeostasis and heightened childhood adiposity in other cohorts [134].

5.3. Epigenetic Effects of Maternal Diet in Pregnancy on Postnatal Growth:

Coppola et al.'s PREMEDI trial randomized 104 pregnant women to either standard care or structured Mediterranean diet (MD) counseling, with 97 completing follow-up. At 24 months, offspring of MD-counseled mothers had a markedly lower incidence of overweight or obesity (6% vs. 30%; risk difference ≈24%) [135]. The trial demonstrated that maternal dietary patterns could influence offspring biology, as MD adherence was associated with increased leptin-gene methylation in cord blood [135]. This randomized controlled evidence complements observational work showing

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diet-induced fetal methylation changes and support the hypothesis that prenatal nutritional quality may influence childhood overweight risk via epigenetic programming of energy-balance pathways.

Yang et al., performed genome-wide placental DNA methylation profiling in a case-control cohort of 60 infants (30 large-for-gestational-age cases, 30 controls), identifying DMPs and DMRs in genes like LEP, ADIPOQ, VSX1, and CDH13 [136]. Leptin pathway DMRs correlated with cord leptin >90th percentile, raising neonatal overweight odds (OR=2.8). This integrates epigenomics with clinical markers, implicating nutrient-induced methylation in fetal adiposity and perinatal overweight risk [136].

5.4. Epigenetic Effects of Maternal Smoking in Pregnancy on Postnatal Weight

In a meta-analysis of 229,158 births from 28 cohorts, Philips et al. found that maternal smoking only in the first trimester of pregnancy was associated with a higher risk of childhood overweight assessed in mid-childhood (5–10 years) (OR ≈ 1.17) [137]. Moreover, continued smoking throughout pregnancy showed dose-dependent increases in preterm birth, SGA, and the highest odds of childhood overweight (OR ≈ 1.42). Reducing cigarette consumption without quitting, offered limited benefits. Paternal smoking, even when mothers were nonsmokers, also increased overweight risk (OR ≈ 1.21). Although epigenetic markers were not measured, prenatal smoke exposure is known to induce persistent methylation changes (e.g., AHRR, GFI1), providing a plausible mechanism linking early gestational exposure to later adiposity [137]. This large meta-analysis reinforces that prenatal smoking, even confined to early pregnancy, may initiate epigenetic programming processes that elevate offspring overweight risk, highlighting the importance of smoking cessation before or very early in pregnancy.

5.5. The Fetal Metabolic Syndrome with Emphasis on Gestational Undernutrition and Overnutrition and Insulin Resistance

The Developmental Origins of Health and Disease (DOHaD) hypothesis proposes that the intrauterine environment programs long-term metabolic outcomes, including insulin resistance and later susceptibility to metabolic syndrome [18]. Central to this framework as noted earlier is the “thrifty phenotype,” which describes adaptive metabolic responses to early-life undernutrition that become maladaptive when followed by postnatal nutritional abundance. On the contrary, gestational overnutrition, characterized as excess maternal nutrient intake that produces “excess nutrient exposure in utero,” disrupts fetal metabolic pathways increasing long-term cardiometabolic susceptibility, has emerged as an equally critical driver of maladaptive fetal programming and insulin resistance [138]. It should be noted that maternal overnutrition in pregnancy may affect postnatal weight in a similar way (Figure 1) [29,34].

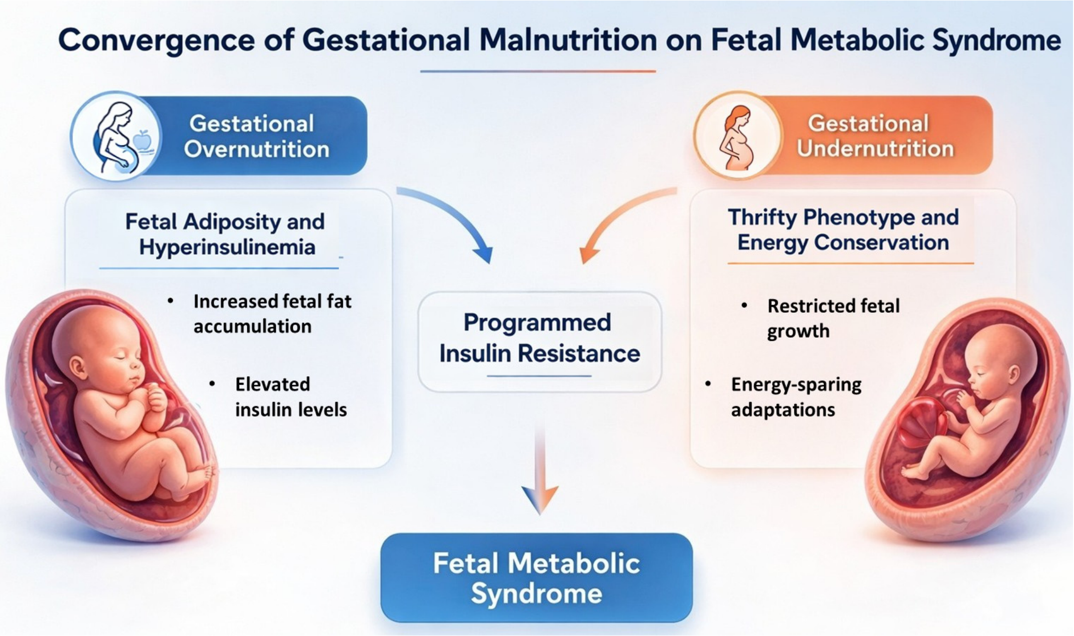

Figure 1. Convergence of Gestational Malnutrition on Fetal Metabolic Syndrome. This illustration depicted how distinct forms of gestational malnutrition [overnutrition (left) and undernutrition (right)] ultimately converge on a shared pathway leading to fetal metabolic syndrome. Gestational overnutrition initiates fetal hyperinsulinemia and increased adiposity, while gestational undernutrition induces a thrifty, energy-conserving phenotype. Despite originating from opposite nutritional states, both trajectories drive the development of programmed insulin resistance in utero, culminating in a unified fetal metabolic syndrome phenotype.

The fetal epigenetic changes induced in pregnancy are also manifested by metabolic changes during adolescence and early adulthood. Follow-up studies demonstrate persistent metabolic alterations in those exposed to gestational overnutrition, including higher fasting glucose and greater odds of overweight or obesity, reflecting long-lasting metabolic vulnerability [36]. Maternal obesity produces adverse metabolomic signatures, particularly elevated lipids and branched-chain amino acids, indicating intergenerational metabolic imprinting [139]. Metabolomics studies further show consistent alterations in lipid-handling and skeletal-muscle pathways among adolescents exposed to intrauterine nutrient excess, confirming biochemical programming of insulin-resistance pathways [72].

In summary: Nutritional imbalances may exert their effects on fetal, neonatal and postnatal adiposity through stable, targeted, and biologically meaningful epigenetic modifications. Whether measured via genome-wide methylation arrays, placental epigenetic mapping, or cord blood profiling, the molecular signatures converge on pathways governing lipid metabolism, adipocyte differentiation, mitochondrial function, and insulin signaling. These mechanistic insights not only deepen our understanding of the developmental origins of excess weight but also position epigenetic biomarkers as potential tools for early risk stratification and possible interventional targeting.

6. Conclusions

Many studies assess the effectiveness of different nutritional programs and diets aimed at controlling childhood obesity. They are generally only of partial success [140]. This review addresses the relatively large number of children that exhibit obesity because of metabolic alterations induced by epigenetic changes originating from undesired events in pregnancy. Most of these factors may cause permanent epigenetic changes which lead to insulin resistance causing childhood and adolescence obesity, and, in adulthood, to type 2 diabetes, hypertension and cardiovascular diseases.

Too often the etiology of obesity in these children is not explored. Nowadays, when a large percent of women of child—bearing age are overweight, have GDM or other pregnancy related complications, we are witnesses to a high percent of overweight and obese children for which ordinary standard treatment is ineffective. Effective treatment is possible only after extensive clinical explorations starting from before and throughout pregnancy and delivery to diagnose (or exclude) prenatal causes responsible for the overweight. Of special importance is the assessment of insulin resistance and other metabolic changes. In such cases we must consider pharmacologic treatment too (i.e., metformin for insulin resistance) in addition to dietary standards and supportive means. Moreover, diagnosis of prenatal etiology may help to prevent or reduce recurrence in subsequent pregnancies.

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Abbreviations

The following abbreviations are used in this manuscript:

BKMR	Bayesian kernel machine regression
BPA	Bisphenol A
BPS	Bisphenol S
DMP	Differentially methylated position
DMR	Differential methylation region
DOHaD	Developmental Origins of Health and Disease
EDC	Endocrine disrupting chemical
EGWG	Excessive gestational weight gain
EPOCH	Exploring perinatal outcomes among children
FGR	Fetal growth retardation
g-comp	quantile g-computation
GDM	Gestational diabetes mellitus
GH-IGF	growth hormone-insulin-like growth factor axis
GRECF	Genomic research of the Chinese famine study
gWQS	generalized weighted quantile sum
HOMA-IR	Homeostatic model assessment of insulin resistance
hsCRP	High sensititvity C-reactive protein
IGFBPs	insulin-like growth factors binding proteins
INMA	INfancia y medio ambiente
LGA	Large for gestational age
MD	Mediterranean diet
PAH	Polycyclic aromatic hydrocarbons
PBDEs	Polybrominated diphenyl ethers
PGDM	Pregestational diabetes mellitus

PGH	placental growth hormone
ppBMI	pre-pregnancy body mass index
PREMEDI	Mediterranean diet during pregnancy study
SGA	Small for gestational age

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