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Early-life programming of adipose tissue

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Abstract

Worldwide obesity is increasing at an alarming rate in children and adolescents, with the consequent emergence of co-morbidities. Moreover, the maternal environment during pregnancy plays an important role in obesity, contributing to transgenerational transmission of the same and metabolic dysfunction. White adipose tissue represents a prime target of metabolic programming induced by maternal milieu. In this article, we review adipose tissue physiology and development, as well as maternal influences during the perinatal period that may lead to obesity in early postnatal life and adulthood. First, we describe the adipose tissue cell composition, distribution and hormonal action, together with the evidence of hormonal factors participating in fetal/postnatal programming. Subsequently, we describe the critical periods of adipose tissue development and the relationship of gestational and early postnatal life with healthy fetal adipose tissue expansion. Furthermore, we discuss the evidence showing that adipose tissue is an important target for nutritional, hormonal and epigenetic signals to modulate fetal growth. Finally, we describe nutritional, hormonal, epigenetic and microbiome changes observed in maternal obesity, and whether their disruption alters fetal growth and adiposity. The presented evidence supports the developmental origins of health and disease concept, which proposes that the homeostatic system is affected during gestational and postnatal development, impeding the ability to regulate body weight after birth, thereby resulting in adult obesity. Consequently, we anticipate that promoting a healthy early-life programming of adipose tissue and increasing the knowledge of the mechanisms by which maternal factors affect the health of future generations may offer novel strategies for explaining and addressing worldwide health problems such as obesity.

Key words: **Adipose tissue: Fetal programming: Developmental origins of health and disease: Maternal obesity**

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Introduction

Adipose tissue is an endocrine and metabolically active organ, which regulates feeding and metabolism in response to energy variations[1,2]. Adipose tissue dysfunction causes obesity, which is associated with metabolic disorders such as the metabolic syndrome, representing one of the most important public health problems worldwide[3].

The prevalence of obesity around the world has increased at an alarming rate, particularly in children and adolescents. The WHO estimates that if current trends continue, the number of overweight infants and young children globally will increase to 70 million by 2025[4].

During childhood, the most rapid weight gain occurs between the ages of 2 and 6 years, and 90 % of children with obesity at the age of 3 years present overweight or obesity during adolescence[5]. Thus, an increasing prevalence of childhood obesity is associated with the emergence of co-morbidities previously considered to be 'adult' diseases, including type 2 diabetes mellitus[6].

Currently, a large number of pregnant women are affected by overweight or obesity[7]. Pregnancy in an obesogenic environment and fetal exposure to malnutrition leads to an increased risk of developing metabolic complications in the future, both for the pregnant women and their offspring[8–10]. Consequently, genetic predisposition, nutrient-regulated gene expression and epigenetic modifications together with environmental factors during intrauterine and postnatal development play an important role in the development of adult diseases[11–13]. This concept, now termed as the 'developmental origins of health and disease' (DOHaD) proposes that the homeostatic system affected during gestational and postnatal development impedes the ability to regulate body

Abbreviations: C/EBP, enhancer binding protein; DOHaD, developmental origins of health and disease; HFD, high-fat diet; IGF, insulin-like growth factor; IUGR, intra-uterine growth restriction; LPD, low-protein diet; ZFP, Zn finger proteins.

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weight after birth, particularly in the face of high energy intake, resulting in adult obesity and metabolic diseases[12,14].

In this line, we have conducted an extensive review based on adipose tissue as an endocrine organ and its physiology and development, with the current knowledge of maternal influences during the perinatal period that may lead to obesity in early postnatal life and adulthood.

The biology of adipose tissue

All animal species, from *Caenorhabditis elegans* to *Homo sapiens*, store energy in the form of fat[15]. Although adipose tissue was classically considered an energy-storing site, it is now widely recognised as an endocrine organ capable of regulating feeding and metabolism through hormone and cytokine secretion[16]. Adipose tissue is composed of adipocytes as well as stromal cells, immune cells, endothelial cells, blood vessels and adipocyte precursors[16,17].

Two well-characterised types of adipose tissue coexist in mammals: white and brown. White adipose tissue is composed mostly of adipocytes containing a large unilocular lipid droplet. Brown adipose tissue specialises in energy expenditure; its adipocytes are rich in mitochondria and contain multiple smaller (multilocular) lipid droplets[2]. Recently, a third type of adipose tissue was described: the inducible 'brown-like' adipocyte, also named 'brite'/'beige', 'browning' or induced brown adipose tissue. Such adipocytes are inserted into the white adipose tissue of human and mice[18,19]. 'Beige' adipocytes have an overlapping, but also a distinct gene expression pattern compared with classic brown adipocytes. Both brown and beige adipocytes express a core programme of thermogenic and mitochondrial genes, including *Ucp1* (uncoupling protein 1), but murine beige cells also express the surface markers CD137 (TNF receptor superfamily member 9) and Tmem26 (transmembrane protein 26). Other marker genes, such as *Zic1* (Zn finger of the cerebellum family member 1), are expressed in classic brown adipocytes but not beige cells[20,21]. To date, the origin or precursor cells of beige adipocytes is still unclear[18].

Adipose tissue distribution is variable between individuals as a function of genetics, sensitivity to hormones, sex and race[2,22]. Additionally, the cellular composition of adipose tissue, adipocyte morphology and the adipose tissue fat depot location define its metabolic and endocrine functions[3,23]. At the molecular and biochemical levels, adipocytes are well equipped with the machinery to respond to both hormonal (for example, insulin) and sympathetic (for example, adrenergic) stimulation[24,25]. Moreover, adipose tissue has high plasticity, being the only tissue in the body that can markedly change its mass after adult size is reached[26].

White adipose tissue is organised in discrete anatomical depots identified as subcutaneous and visceral adipose tissue; the first is distributed below the skin, while visceral adipose tissue is located in the trunk cavity in humans and mice[2]. During times of increased food intake and/or decreased energy expenditure, surplus energy is deposited efficiently in white adipose tissue in the form of neutral TAG. When food is scarce and/or energy expenditure requirements increase, lipid reserves are released to provide fuel for energy generation. TAG from adipose tissue break down into glycerol and fatty acids, which are transported in the blood to the liver, muscle and brown adipose tissue, where they are used in fatty acid oxidation. As such, white adipose tissue plays a key role not only by ensuring efficient energy storage but also by rapidly mobilising lipids to ensure peripheral demands through a coordinated endocrine regulation between the nervous system[16].

On the other hand, brown adipose tissue is distributed in axillary, cervical, perirenal, periadrenal and interscapular regions, actively participating in basal and inducible thermogenesis[27]. For a long time, it was thought to be present only in rodents and newborn humans. However, recent investigations using ^{18}F-fluorodeoxyglucose positron emission tomography after cold exposure, lactation and exercise re-discovered the presence of brown adipose tissues (brown adipose tissue and induced brown adipose tissue) in adult humans[27–29].

Several studies demonstrated that increasing brown/beige adipose mass could be a potential therapeutic approach to treat obesity[29]. The confirmation that adult humans display highly metabolically active brown adipose tissue raises the possibility of controlling its growth and/or energy expenditure in obesity[30,31]. Nevertheless, this conception may be limited by the uncertainty regarding the identity and origins of adipocytes from different depots and poor information available about how obesity-associated changes in cellularity influence white adipose tissue plasticity[3].

Development of adipose tissue

Cellular expansion of adipose tissue is associated with hypertrophy (increase in size) and hyperplasia (increase in number, 'adipogenesis'). Both phenomena occur in normal growth throughout life and during obesity development[15,32]. Adipogenesis is the result of the differentiation of new adipocytes from precursor cells in the adipose tissue. Adipogenesis comprises several steps orchestrated by a transcriptional cascade involving the nuclear PPARγ: the 'master regulator' of adipocyte differentiation along with the members of the enhancer binding proteins family (C/EBP), bone morphogenetic proteins (BMP) and Zn finger proteins (ZFP). Two interesting reviews on this field are by Ma *et al.*[33] and Ghaben & Scherer[34].

Both brown and white adipocytes start their development *in utero*. However, the timing and rate of adipose tissue formation varies somewhat between species[35]. In humans, Poissonnet *et al.*[36,37] found that adipose tissue (in the form of fat lobules with no lipid storage) first appears during early pregnancy in both sexes, between 14 and 24 weeks of gestation (start of the second trimester). The precise timing may depend to some degree on fetal size or weight, with larger fetuses developing identifiable adipocytes earlier than smaller ones. By the third trimester (28 weeks), adipose tissue depots are already established[37]. In particular, the first evidence of brown adipose tissue depots is from 20 weeks of gestation, with a maximal time of 26 weeks, being stabilised at 35 weeks[38].

In rodents, adipose tissue mainly develops between late gestation and 4 weeks of postnatal age[39]. A study in the mouse model called 'AdipoChaser' – a system that can detect the already

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present adipocytes from those that are newly formed – revealed that subcutaneous adipose tissue development occurs early during embryogenesis, in embryonic days 14–18. In contrast, epididymal adipocytes preferentially differentiate postnatally[40]. Another study using sensitive reporters revealed the expression of adipose-specific markers in the subcutaneous region as early as embryonic days 16·5–17·5, after lipid-filled subdermal adipocytes. This research also shows that the epididymal adipose tissue was formed postnatally[41]. Both lines of evidence coincide with Han *et al.*[42], who demonstrate that precursor cells are not found in the nascent epididymal pad until postnatal day 4.

Adipose tissue in both humans and rodents remains to some extent expandable later in life[43]. Generally, adipocyte expansion ceases at adolescence. In humans, roughly 8 % of adipocytes turn over approximately every year, while in mice, 0·6 % of adipocytes are renewed each day[43,44]. Interestingly, the absolute number of turn-over adipocytes in individuals with obesity is approximately twice compared with lean individuals[43]. However, the major development of adipose tissue coincides with plastic periods of pregnancy and lactation, when hormonal, nutritional and epigenetic signals influenced by the mother probably programme permanent changes in the offspring's adipose tissue[45].

Adipose tissue as an endocrine organ

Adipose tissue secretes numerous peptides, hormones and molecules (called adipokines), which act in auto-, para- and endocrine manners. Adipokines participate in signalling the functional status of the adipose tissue to target cells in the brain, liver, pancreas, vasculature, muscle and other tissues[46,47] (Fig. 1).

Adipokines participate in the regulation of several physiological processes in the adipose tissue and at a systemic level. Adipokine secretion, mainly leptin and adiponectin, modulate appetite, fuel metabolism, innate immune function and reproduction (Table 1). Moreover, abnormal adipokine secretion contributes to a spectrum of obesity-associated diseases[34]. The evidence of hormones and growth factors that modulate the adipose function is summarised in Table 2.

Hormonal signals during pregnancy modulating fetal growth and adiposity

Due to the obesity epidemic, attention has turned to potential influences of maternal obesity (BMI ≥30 kg/m^2) and the risk of disease in the offspring[48]. Maternal obesity and diabetes are associated with increased birth weight, excessive nutrition in neonates, and rapid 'catch-up growth' that predispose the offspring to fat accumulation[49,50]. The mechanisms linking pregnancy obesity to altered fetal growth and programming of adult disease are not well established. However, during the gestational period and birth, studies have shown a correlation between maternal hormones and birth weight[51].

An important element associated with birth weight in the function of gestational age is insulin-like growth factor (IGF)-1[52]. Maternal IGF-1 is stimulated by hormonal signals, promoting placental growth and function[53,54]. In both animals

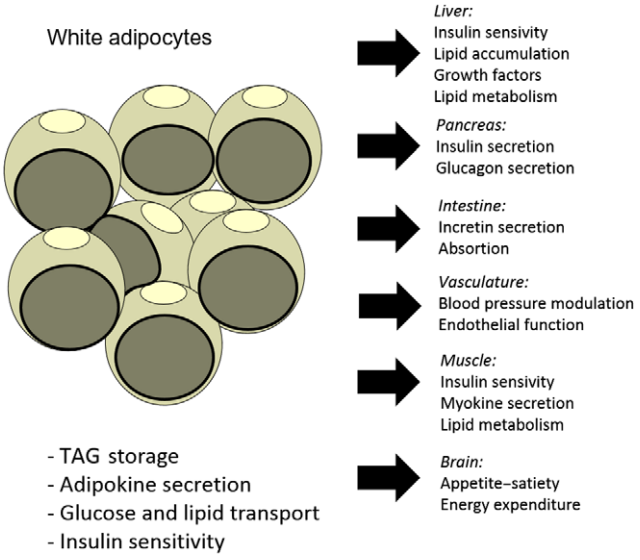


Fig. 1. Interaction between white adipose tissue with other organs contributes to maintaining energy balance. The development of either normal or altered adipokine secretion may contribute to whole-body homeostasis during health and disease.

and humans, circulating IGF-1 is reduced in intra-uterine growth restriction (IUGR) neonates[52,55]. However, when IGF-1 is administered to mothers of IUGR fetuses, it promotes placental nutrient transfer to enhance fetal growth. IGF-1 levels are correlated with weight gain and increased nutrient intake after intra-uterine nutrient deprivation[52]. Notably, maternal IGF-1 treatment in the late pregnant ewe is associated with enhanced glucose delivery to the fetus[56]. This was also observed in a mouse model of IUGR, where placental GLUT expression was increased after an intraplacental injection of adenovirus-mediated IGF-1, thus restoring fetal weight[57]. In addition, reduced maternal circulating IGF-1 is associated with small-for-gestational-age and growth-restricted babies[58]. Therefore, tissues chronically depleted of insulin and IGF-1 throughout fetal life and suddenly exposed to increased concentrations of those hormones shortly after birth may counteract the actions of insulin by developing insulin resistance as a defence mechanism against hypoglycaemia[57,59].

Obesity in pregnancy is characterised by elevated maternal serum insulin and leptin hormones that also stimulate placental amino acid transporters *in vitro*[57]. High levels of these hormones activate placental insulin/IGF-1/mTOR (mammalian target of rapamycin) and leptin signalling pathways, thus increasing placental amino acid transport capacity and determining fetal overgrowth in a maternal obesity mouse model[60].

Additionally, leptin has a broader range of actions, particularly during growth and development[61]. Besides adult[62] and fetal adipose tissue[63], the placenta is an important site of leptin production[64]. The human leptin gene has a placental-specific upstream enhancer, which mediates its placental expression[61,65]. Furthermore, leptin may play a role in implantation, placental endocrine function and fetal development[66]. Circulating maternal leptin increases during pregnancy and evidence indicates that leptin may participate in placental angiogenesis, immunomodulation, nutrient transport and growth[64,66]. Co-localisation of leptin

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Table 1. Adipokines and their potential role in adipose tissue programming

Adipokine	Biological process	Potential role in adipose tissue programming
Adiponectin	Increases insulin sensitivity, antidiabetic and anti-inflammatory effects[161,162]	Elevated adiponectin in lean pregnant women limits placental nutrient transfer and fetal growth compared with pregnant women with obesity. Low levels of adiponectin in mothers with obesity are associated with LGA newborns[60,79]
Complement factor D/adipsin	Promotes lipid accumulation and adipogenesis; improves β-cell function[163,164]	Maternal obesity and HOMA-IR correlate with higher levels of adipsin and HOMA-IR in cord blood[165] Adipsin correlates positively with BMI in early and late normal pregnancy and increases in pre-eclamptic women[166]
IL-6	Pro-inflammatory cytokine; increases insulin resistance[167,168] The placenta is considered the major site for IL-6 secretion into both maternal and fetal circulation during pregnancy[169]. IL-6 stimulates fatty acid transfer from maternal circulation to the placenta[170]	Maternal exposure to IL-6 during pregnancy in rats increases body weight, adipose tissue and insulin resistance in male offspring, while female offspring show increased adipose tissue, stress response and increased plasma leptin[171] Plasma IL-6 is higher at day 18 of gestation in dams with obesity induced by HFD, coinciding with an increase in fetal hepatic TAG accumulation[172]
IL-10	Anti-inflammatory effects[173]	Pregestational diet-induced obesity in mice increases IL-10 levels in plasma, but these levels are normalised at day 18 of gestation[172]
Leptin	Modulates satiety in the hypothalamus; increases energy expenditure, growth induction[174,175]	Pregestational obesity in a mouse model increases serum leptin during pregnancy[172] Leptin levels in healthy pregnancy are associated with adequate fetal growth. However, the serum leptin profile of women with obesity is altered during pregnancy[176] Leptin serum levels are correlated with BMI and adiposity in children, young, and adults throughout life[50]
MCP-1	Monocyte/macrophage recruitment; proinflammatory effects[177,178]	MCP-1 is increased in mothers with obesity[179]
Resistin	Proinflammatory; increases insulin resistance in rodents[180] Resistin expression is increased in human adipose tissue, and positively correlates with body fat content. However, the exact function of adipose tissue-derived resistin in humans is unknown[181]	Serum resistin levels are increased during pregnancy[182] Resistin levels of maternal serum, umbilical cord blood and placenta are decreased in mothers with obesity[183] Resistin may play a role as an inhibitory effect on adipogenesis[184]. Thus, a lower resistin level in mothers with obesity may reduce the inhibitory effect on adipogenesis and increase adipose tissue in fetus[183]
RBP4	Factor involved in development of visceral fat distribution, dyslipidaemia and insulin resistance[185,186]	RBP4 concentrations are similar between normal-weight and pregnant women with overweight/obesity[187]. However, high RBP4 and a higher risk of GDM have been shown in women >35 years old[188] Meta-analysis studies relating adipokines to GDM risk reported inconsistent data for RBP-4[189]. Cord blood RBP4 is higher in offspring from GDM pregnant women[190]
TNF-α	Pro-inflammatory cytokine participates in systemic inflammation and insulin resistance development in obesity[191,192]	Rat males of mothers exposed to TNF-α treatment during pregnancy have increased body weight, adipose tissue and fasting insulin. Female offspring have increased adipose tissue and plasma testosterone[171] Maternal obesity increases TNF-α gene expression in the labyrinth zone of rat placentation site, equivalent to the villous tissue[193]

LGA, large for gestational age; HOMA-IR, homeostatic model assessment of insulin resistance; HFD, high-fat diet; MCP-1, monocyte chemoattractant protein 1; RBP4, retinol binding protein 4; GDM, gestational diabetes mellitus.

and its receptor in the syncytiotrophoblasts/cytotrophoblasts (one of the three layers of placenta villi) at the maternal interface is evidence that placental leptin is an important fetal growth factor[66]. Therefore, the temporal co-expression of the long isoforms of the leptin receptor and its ligands in mesenchymal tissues during fetal development leads to leptin acting as a paracrine or autocrine factor during fetal life[61]. Supporting that evidence, placental leptin concentration is increased in small-for-gestational-age newborns and correlates negatively with placental weight. Moreover, the leptin receptor isoforms LEPRα (short form) and LEPRβ (long form) are differentially expressed in the placenta according to birth weight[67]. The umbilical cord leptin correlates positively with placental weight and the newborn's weight[67], explaining up to 21 % of birth weight variation[68]. In addition, umbilical cord blood leptin has a significant correlation with fetal insulin resistance[69]. Thus, both IGF-1 and leptin have crucial roles in activating pathways that lead to the increase of placental amino acid transport capacity and may importantly determine fetal overgrowth in maternal obesity.

Furthermore, both insulin and leptin may also activate adipogenesis. Hence, maternal obesity and elevated circulation levels of insulin and leptin may enhance adipogenesis and lipogenesis, resulting in higher white adipose tissue mass and adipocyte hypertrophy in offspring[70,71]. In agreement with this concept, increased circulating leptin levels in macrosomic fetuses and decreased leptin levels in growth-restricted fetuses have been

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Table 2. Endocrine regulators of adipose tissue physiology and their potential role in the developmental origins of health and disease (DOHaD)

Hormone/growth factor	Effect on adipose tissue	Potential role in DOHaD
Insulin/IGF	Promotes preadipocyte differentiation Accelerates lipid accumulation, activates lipogenic enzymes, promotes GLUT-4-mediated glucose transport[194,195]	Reduced serum IGF-1 levels during pregnancy are associated with fetal growth retardation. After birth, IUGR babies deprived of insulin or IGF-1 during fetal life exhibit altered glucose metabolism and hypertension during adult life[54,56] In a rat model, offspring from mothers who were fed a low-protein diet during pregnancy have reduced plasma levels of IGF-1 postnatally until they reach puberty[196]
FGF	FGF-1, -10, -16 and -19 have been involved in adipose development. FGF-10 shows significant mitogenic activity in primary preadipocytes[197,198]	Serum concentrations of FGF-2 are higher in GDM mothers and their macrosomic babies[199]
Thyroid hormones	T_3 regulates adipogenesis, lipogenesis and lipolysis *in vitro* as well as *in vivo* through the THRα-1 receptor. Mutations in the THRα-1 gene induce increased body fat and visceral adiposity[200,201]	fT_3 is correlated between maternal and fetal serum and increased with maternal obesity[202] Maternal energy restriction in pregnant rats decreases circulating T_3 in male offspring and Dio2 mRNA in WAT of male offspring at postnatal day 25. Both effects were normalised by leptin treatment during lactation[203] Maternal HFD feeding in non-human primates modulates the fetal thyroid axis and gene expression, decreasing genes necessary for thyroid hormone production in the fetal thyroid and hypothalamus, leading to decreased fetal fT_4. Concomitantly, THRβ-1 is increased in the fetal liver, presumably through epigenetic mechanisms[204]
GH	GH promotes differentiation and sensitises the cells to the mitogenic effects of IGF-1 in 3T3F44-2A preadipocytes[205] Obesity is associated with reduced levels of GH NEFA and GH integrate a feedback loop. An increase in NEFA blocks GH secretion, influences fat distribution and decreases central obesity[206]	Maternal levels of placental GH positively correlate with fetal birth weight. In SGA pregnancies, GH secretion is reduced[207] Infants with low birth weights present GH resistance and tend to have lower circulating GH as young adults[208] Passive immunisation of the fetal rat against GH-releasing hormone permanently alters adult GH secretion[209]
Glucocorticoids	*In vitro*, dexamethasone (synthetic analogue of glucocorticoids) induces preadipocyte differentiation and increases lipolysis[210] *In vivo* deletion of glucocorticoid receptor promotes diet-induced inflammation and macrophage infiltration in fat pads[211] Cortisol excess increases central adiposity (both subcutaneous and visceral adipose tissue)[212] 11β-HSD2, which converts (inactive) cortisone to (active) cortisol, is overactive in obesity and could accentuate central adiposity, lipid synthesis, dyslipidaemia, inflammation and insulin resistance[213,214]	Maternal exposure to dexamethasone increases adipose tissue and plasma leptin in female offspring[171] Moderate reduced nutrient intake in pregnant baboons increases maternal and fetal circulating cortisol, increasing cortisol in the adipose tissue of the female and the liver of the male offspring[215] Placental 11β-HSD2 methylation and protein expression is lower in SGA *v.* AGA[216], and methylation patterns of placental 11β-HSD2 correlate with infant growth and neurodevelopment[217]
Testosterone	Normal testosterone levels limit fat mass, whereas its deficiency increases intra-abdominal fat[218]	Testosterone exposure during pregnancy has been associated with: increased fat depots in monkeys[219], increased body weight, hypertension, gut microbiota dysbiosis, higher adiponectin and leptin expression in WAT in rats[220], and reduced adipogenesis in visceral adipose tissue of female sheep offspring[221]
Oestrogen	Oestrogen increases subcutaneous adipose tissue (especially gluteal) and limits visceral adipose tissue. Adipose tissue-specific deletion of ERα increases total body fat, due to an increase in gonadal adipose tissue in female mice Oestrogen receptor is necessary for promoting the identity and differentiation of white adipose progenitor cells[222,223]	HFD feeding during late gestation in mice increases ERα expression in visceral adipose tissue, showing an increase in subcutaneous fat mass, but not in visceral fat mass[224] Maternal obesity decreases ERα and ERβ in the visceral adipose tissue of female offspring, which present increased adiposity and adipocyte hypertrophy[225]
hCG	hCG *in vitro* has a direct and positive effect on both proliferation and differentiation of human preadipocytes. hCG also regulates leptin secretion in human adipose tissue[226,227]	hCG is negatively associated with pregestational BMI[228]. hCG stimulates angiogenesis *in vitro* through interplay with FGF, leptin, resistin, adiponectin and IL-6[229]

IGF, insulin-like growth factor; IUGR, intra-uterine growth restriction; FGF, fibroblast growth factor; GDM, gestational diabetes mellitus; T_3, triiodothyronine; THRα-1, thyroid hormone receptor α-1; fT_3, free triiodothyronine; Dio2, deiodinase iodothyronine type II; WAT, white adipose tissue; HFD, high-fat diet; fT_4, free thyroxine; THRβ-1, thyroid hormone receptor β-1; GH, growth hormone; SGA, small for gestational age; 11β-HSD2, 11-β hydroxysteroid dehydrogenase type 2; AGA, appropriate for gestational age; ERα, oestrogen receptor α; ERβ, oestrogen receptor β; hCG, human chorionic gonadotropin.

reported[72]. The significance of altered fetal leptin levels in circulation is relevant for fetal physiology, since those levels are proportionate to insulin levels and adiposity[73]. These findings align with the fact that fetuses from mothers with obesity develop insulin resistance *in utero* and are born with increased body fat compared with newborns from lean, healthy mothers[69]. Importantly, leptin treatment from postnatal days 3–13 in a rodent model of maternal undernutrition resulted in a transient

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slowing of neonatal weight gain in the offspring and normalised energy intake, locomotion activity, body weight, fat mass, and fasting plasma glucose, insulin and leptin concentrations[61]. Consequently, it is possible that increased circulating concentrations of maternal hormones, such as leptin and insulin, constitute a mechanistic link between maternal overweight or obesity and fetal overgrowth, mediated by modulation of placental nutrient transport and placental growth[74].

Adiponectin may also play a role in modulating growth and adiposity during pregnancy[75,76]. There are controversial reports on which tissue produces adiponectin during pregnancy. In physiological conditions (non-pregnant), adiponectin is produced exclusively in the adipose tissue. Reports indicate that during pregnancy, the placenta secretes adiponectin[77]. In contrast, other studies have not confirmed these findings[78] and suggest that it is likely that the adiponectin influencing placental function predominantly originates from the maternal adipose tissue[75].

The role of adiponectin in pregnancy is related to placental transporters[75,76]. In maternal obesity, adiponectin levels are reduced and placental amino acid nutrient transporters are up-regulated[79]. Interestingly, adiponectin has insulin-sensitising actions in liver and muscle[75]. However, in primary human trophoblast cells, adiponectin attenuates insulin signalling. As a result, adiponectin inhibits insulin-stimulated amino acid transport, which has an important role in placental nutrient transport and fetal growth during pregnancy[79]. In addition, adiponectin supplementation in dams with obesity from embryonic day 14·5 to 18·5 reverse the adverse effects of maternal obesity on placental function and fetal growth[76].

Another important hormone produced during pregnancy is human chorionic gonadotropin. Its concentrations increase exponentially during the first 2 months of pregnancy and decrease abruptly to reach basal values at the end of the third month, a period in which a significant change in the depot-specific fat mass is evident, and, particularly, an accumulation of fat mass to cover the energy demands of both the fetus and the mother occurs[80]. However, little is known concerning the role of human chorionic gonadotropin in adipose tissue metabolism, especially when this hormone is actively secreted.

During pregnancy, other hormones such as the sex hormones progesterone, oestrogens and oestradiol play a key role in adipose tissue metabolism[51,81]. However, the role of hormonal status during pregnancy is still a broad field to investigate. Further elucidation about the physiology of actively secreted hormones between the mother and progeny during pregnancy may offer novel strategies for therapy and prevention of birth weight alterations in the offspring.

Nutritional signals modulating fetal growth and adiposity during pregnancy

It is well know that both over- and undernutrition result in endocrine changes associated with adult adiposity[11]. These opposite paradigms have been used to study the long-term effects of nutritional manipulations during prenatal and early postnatal life. Several studies in both human and mouse models have demonstrated that perturbation of circulating factors, such as nutrients and/or hormones induced by diet during fetal development, increase the risk of obesity during childhood and adulthood[82,83]. Furthermore, other investigations have shown that the programming of appetite dysregulation contributes to the obesity phenotype in IUGR offspring[74]. IUGR and small-for-gestational-age newborns typically present accelerated postnatal growth, defined as 'catch-up' growth, within the first years of life[84]. This suggests that accelerated infant and childhood weight gain is associated with increased energy intake and diminished satiety response[85]. In addition, Desai *et al.*[86] found that IUGR rats present hypertrophic adipocytes and increased *de novo* lipogenesis, factors that predispose increased fat storage. Moreover, compelling evidence indicates that faster infant growth in humans is associated with obesity later in life, independently of country income, gestational age, birth weight or breast-feeding[84].

Maternal obesity, excessive nutrition and accelerated neonatal growth have been shown to sensitise offspring to obesity[87]. In a rodent model, maternal high-fat diet (HFD) during pregnancy increased maternal adiposity and circulating leptin and decreased adiponectin, causing a 43 % increase in fetal growth compared with controls[73]. Male neonates from mothers fed a HFD before and during gestation and lactation exhibit a rapid weight gain during lactation, concordant with a key period of adipose tissue development in rodents[39]. In addition, male offspring from HFD mothers have higher expression of Zn finger protein 423 (*zfp423*) and lower DNA methylation of its promoter in epididymal fat progenitors compared with control lean offspring, coincidentally with enhanced adipose tissue differentiation in this period[45]. Moreover, adult male offspring from HFD mothers are predisposed to fat accumulation, showing increased visceral, gonadal and perirenal fat depots, together with hyperleptinaemia. The perirenal adipose tissue depot exhibits elevated sterol regulatory element-binding protein 1 (SREBP1), fatty acid synthase (FAS), leptin, and diminished PPARγ mRNA levels[71]. Further, maternal HFD during pregnancy alone programmes increased offspring adiposity with normal body weight, whereas maternal HFD during lactation increases both body weight and adiposity[87]. The reasons behind this discrepancy are not understood but may depend on differences in the nutritional intervention such as the duration of maternal HFD feeding, lipid content in diet, and/or in the different genetic background of rodents.

Adult rat offspring from mothers obese by cafeteria-diet feeding during gestation and lactation exhibit an increase in adipose tissue TAG content with elevated lipogenic enzyme activities, along with abnormalities in fatty acid composition[88]. These findings indicate that perinatal exposure to a diabetic milieu characterised by increased glucose and/or insulin levels can programme developmental processes such as adipogenesis[74].

The consumption of fructose-rich diets is on the rise and is thought to be associated with obesity and cardiometabolic diseases. Recently, fructose has been used as a sweetener in many food items[89]. Feeding pregnant C57BL/6J dams with fructose at 10 % (w/v) (similar to most fructose-sweetened soft drinks) makes the offspring present different risks for disease profiles

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in a sex-dependent manner. Males become hypertensive and develop insulin resistance, while females develop additional abnormalities including obesity, increased adiposity, fatty liver, high serum leptin and low serum adiponectin[90]. It is also known that male and female placentas react differently to the perinatal environment, and differential effects of fructose on the placental transport system have been reported[91]. For example, male placentas are glucocorticoid resistant, whereas female placentas respond to different glucocorticoid levels by altering cortisol metabolism, placental protein/gene expression, placental growth factor pathways and placental immunity[92,93].

The influence of overnutrition is not the only nutritional factor determining the programming of adipose tissue dysregulation. For example, the offspring of low-protein diet (LPD)-fed dams during gestation and lactation have persistent smaller adipocytes due to a decrease in adipose cell size[74,94]. However, in adulthood, offspring from LPD-fed mothers exhibited increased mRNA expression levels of C/EBPα and PPARγ, suggesting enhanced adipogenesis[95]. Furthermore, this model also exhibited increased adipose tissue expression of miRNA-483-3p, known to regulate *in vitro* differentiation and lipid storage of adipocytes. In contrast, the offspring of LPD-fed dams, which had 50 % food restriction during gestation, exhibited low birth weight and enhanced adipogenic factors, such as PPARγ and C/EBPα, and presented small adipocytes[94]. Nevertheless, if maternal protein was 70 % food restricted during gestation, the persistent feature was the appearance of hypertrophic adipocytes[96]. The reasons of these findings are completely uncertain. However, according to the DOHaD concept, a single genotype could produce many phenotypes, depending on intervention characteristics and timing, environmental influences and/or epigenetic changes, leading to alterations in the fetus or neonate in long-term programming and responses particularly against a metabolic challenge in adulthood[97,98].

Epigenetic changes during pregnancy modulating fetal growth and adiposity

Studies in both human and animal models provide evidence of programmed adiposity and metabolic diseases resulting from early nutritional exposures, suggesting that epigenetic modification may be a major contributing factor[99].

Indeed, maternal (and/or paternal) perinatal nutritional interventions can cause epigenetic modifications such as differential gene promoter methylation (i.e. in CpG sites), chromatin remodelling, histone acetylation/methylation, and post-transcriptional changes such as differential mRNA expression in offspring[74,100]. Notably, exposure to either maternal famine or obesity reduces DNA methylation of the imprinted IGF-2 gene in the offspring. Studies in old adults who were prenatally exposed to famine showed hypomethylation on the IGF-2 gene, and hypermethylation in two major obesity-related non-imprinted genes: TNFα and leptin[101]. In addition, placental leptin gene methylation is increased in gestational diabetes[102]. Moreover, alterations in methylation at specific sites in weight loss have been observed[103], and several associations between methylation marks at birth and later-life obesity were found[104,105]. Other reports have evidenced DNA methylation of genes such as IGF-2/H19 in the offspring of mothers with an unbalanced diet during pregnancy[106,107]. These modifications in methylation are associated with increased weight, waist circumference, BMI, blood pressure, fat accumulation, and obesity in the offspring[108].

On the other hand, HFD feeding during pregnancy in mice increases the expression of *zfp423*, a key transcription factor responsible for adipogenic lineage commitment during fetal development in the offspring. Accordingly, repressive histone methylation (H3K27me3) was lower in the *zfp423* promoter in fetal tissues from dams with obesity[109]. Offspring from dams with obesity, which were fed a HFD from birth until 3 months of age, showed an increased proportion of adipocyte progenitor density compared with mice fed a HFD postnatally but unexposed to maternal obesity[45]. This evidence suggests that maternal obesity may epigenetically limit the expansion capacity of offspring adipose tissue. In addition, alterations in DNA methylation of CpG sites and CGI shores of pro-adipogenic factors, such as Zfp423 or C/EBP-β, have also been demonstrated in young rats from mothers with obesity during pregnancy[110]. Obesity-prone weanling rat from dams with induced obesity by intragastric feeding of a HFD present greater *ex vivo* adipocyte differentiation, associated with increased mRNA expression levels of PPARγ and C/EBPβ, together with alterations in DNA methylation of CpG sites[110].

Other perinatal food interventions can cause epigenetic modifications in offspring. For example, adult mice from LPD-fed dams presented removal of CpG methylation in the leptin promoter in white adipose tissue, affecting leptin expression dynamics in response to a meal[111]. A LPD during pregnancy also produces an increase in miRNA-483-3p expression levels with a decrease in GDF3 (growth differentiation factor 3; a member of the bone morphogenetic protein/transforming growth factor β (BMP/TGF-β) family) protein content, a factor that impairs late stages of adipocyte differentiation in rat offspring[94].

Maternal microbiota modulates fetal growth and adiposity

It has been largely demonstrated that the gut microbiota plays a key role in health and disease, including obesity and its metabolic complications[112,113]. However, the presence of an intrauterine microbiome is still under debate. While certain studies have shown the presence of bacteria in placenta[114–116] and amniotic fluid[116], others attribute these findings to sample contaminations[117,118]. To date, a newborn's colonisation at birth is the only mechanism of neonatal microbiome origin[119].

Several maternal nutritional and pathological conditions, including maternal obesity, have been associated with changes in maternal and neonatal gut-microbiota dysbiosis, which could affect microbial composition and promote metabolic disturbances in the offspring (reviewed in Calatayud *et al.*[120]). A study by Koren *et al.*[121] that analysed the faecal microbiota in ninety-one healthy pregnant women from the first to the third trimester found that significant changes in microbial diversity

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occurred during the third trimester, whereas in early pregnancy, the microbiota was similar compared with the normal controls of the Human Microbiome Project. Interestingly, these changes are associated with the increase in proteobacteria population, which correlates with levels of proinflammatory cytokines interferon-γ, IL-2, IL-6 and TNF-α[122,123]. In addition, the transference of the microbiota from healthy pregnancies in the third trimester to germ-free mice increased adiposity, insulin resistance and inflammation compared with mice receiving first-trimester microbiota[121]. Therefore, the gut microbial community may have a critical role in maternal metabolic adaptations, which may influence fetal growth and development during normal pregnancy. Conversely, another study demonstrated that gut microbial diversity was stable throughout pregnancy[124]. Although the altered composition of gut microbiota is still controversial among different studies, discrepancies may be partly attributed to genetics, BMI, maternal nutrition and/or gestational age of the woman studied[122].

In an animal model study, about twenty-six genera of gut-microbiota were significantly different in HFD-fed pregnant mice compared with normal diet-fed mice[125,126]. Other studies also analysed the association between gut-microbiota composition and maternal metabolic parameters, and its changes with maternal preconceptional diet[127,128]. Furthermore, the increased *Staphylococcus* population positively correlated with increased plasma cholesterol levels, whereas a decrease in *Bacteroides* was associated with lower HDL-cholesterol and higher serum TAG levels[129]. Thus, these alterations in the gut microbiota could predict the changes in metabolic pathways[122]. Interestingly, a significant reduction in *Bacteroides* was also observed in the neonatal gut microbiota from HFD-fed mothers during gestation, which persisted until 6 weeks of age[130]. Hence, the increased risk of obesity for children from mothers with obesity could be partially explained by the transmission of maternal obesogenic intestinal microbes[131].

Maternal weight has been found to be a major influencing factor determining milk bacterial composition[131]. Higher abundance of *Staphylococcus aureus* was reported in breast milk over the first 6 months of lactation, as well as that of *Lactobacillus* in the first month of women with obesity compared with mothers with normal weight[132,133]. Interestingly, high levels of *S. aureus* are also found in the gut microbiota of overweight children[134]. However, the concrete effects of these findings are still unclear. Therefore, future research is needed to determine whether milk microbial population is associated with maternal and offspring adiposity.

Major changes in maternal microbiota during pregnancy have also been shown to correlate with adipose tissue development in humans[37], in which, as described above, alterations could be determining adipose tissue dysfunction in both the mother and the offspring[50]. Additionally, modification in specific metabolic hormones including insulin, gastric inhibitory polypeptide, and adipokines were also found to be correlated with alterations in bacterial population, supporting a connection between microbial diversity and metabolic hormones during pregnancy[135].

Overweight and obesity during pregnancy result in obvious changes in microbiota composition and concomitant metabolic disorders in the mother. Maternal microbial transfer to the neonate could represent the first colonisation of gut microbiota in early life. Therefore, gut microbiota might be a critical factor supporting the DOHaD hypothesis and play a crucial role in programming. More studies oriented to characterise human microbiota during pregnancy and its complications – and associations with its effects on fetal development – will surely shed light on the potential role of the microbiome in programming obesity in childhood and adulthood.

Adiposity regulation in the early postnatal period

In rodents, adipose tissue development is particularly active during the perinatal period, especially the last week of gestation and early postnatal life[36,37,39]. Offspring from undernourished or overnourished mothers present alterations in the adipose tissue, such as changes in fat distribution/composition, enhanced adipogenesis, altered hormone levels and sensitivity to them (especially the glucocorticoid system), environmental influences, and epigenetic mechanisms, all of which modify adipose tissue programming during the perinatal period[99,136].

Critical periods to body composition establishment during the neonatal period and early childhood may be predicted by maternal pre-pregnancy BMI, adiposity, gestational weight gain, maternal nutrition, maternal TAG concentrations, maternal smoking, and inflammation during pregnancy[51,137]. About 15–45 % of babies born to diabetic mothers are macrosomic. Weight gain rate during the first year, particularly peripheral fat, is an indicator of trunk fat mass and affects the rate of weight gain during the first 6 months of life[11]. The molecular mechanisms driving the correlation between excess weight gain in the first 6 months and later obesity remain unknown.

Several studies have associated early infant growth with later risk for overweight, suggesting that early infancy is a crucial window of metabolic programming[8]. It is even suggested that the first weeks and months of life are particularly associated with later weight status[138], which are a critical time when metabolic programming can occur, similar to the *in utero* period, because the infants' organs still maintain considerable plasticity for adaptation to nutritional and environmental exposures[137,139]. Thus, this early age provides a critical opportunity for interventions directed to have an impact on future metabolic health.

Breast milk represents the main source of nutrients in the first months of life for breastfed infants, providing different nutrients and bioactive factors, especially hormones and growth factors such as leptin, ghrelin, insulin and IGF-1. It also plays a role in food intake regulation, metabolism and body composition[140–142].

Breast milk composition is dynamic and variable among women. Fat is a major digestible component, comprising over 50 % of the energy of breast milk[143]. Macronutrient intake, hormonal and behavioural mechanisms related to breast milk composition (i.e. protein, PUFA, oligosaccharides, cytokines and hormones, in particular leptin, adiponectin and resistin), together with the breast-feeding practice itself, can influence the infant's feeding behaviour and regulation of growth and appetite control later in life. On the other hand, serum levels of leptin vary dramatically during intra-uterine and early

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postnatal life, with a 5- to 10-fold increase in leptin occurring between postnatal days 4 and 10 in female mice[144]. Moreover, breast milk leptin may participate in postnatal development, possibly contributing to elevated circulating levels of this hormone in the neonate[61]. However, research is needed to confirm the hormonal biological effects.

In addition, fatty acid composition of human milk is influenced by maternal diet. For example, *trans*-fatty acid content in the maternal diet increases the risk of increased adiposity in the neonate, and the associated chronic diseases later in life. Overall maternal dietary *trans*-fatty acid intake may influence adiposity in mothers and their infants[145]. However, several studies support the hypothesis that breast-feeding might confer protection against obesity later in life[146,147]. A meta-analysis showed that the length of the breast-feeding period was associated with a decreased risk of childhood obesity. Children breastfed for ≥7 months were significantly less likely to have obesity compared with those breastfed <3 months[148]. However, other studies have reported conflicting results[149,150], which could be due to forms of interpretation depending on the type of study, postpartum period, group size, or a dose-dependent effect of breast-feeding duration on the prevalence of obesity. Moreover, various studies agree on the need to expand the research about the effects of breast milk composition on childhood adiposity and overweight[145,147]. Interestingly, obesity-prone rat offspring artificially raised by intragastric canula ('pup in the cup' model) with a high-carbohydrate milk formula exhibited hyperinsulinaemia, hypertrophic adipocytes and enhanced adipose tissue lipogenic enzyme activities compared with pups fed rat milk where the major source of energy was fat[151].

A recent study evidenced that prolactin, one of the most abundant hormones secreted during lactation and present in high quantities in maternal milk[152], was reduced in dams fed a HFD during lactation, showing altered mammary gland structure and function compared with control-fed dams. Moreover, offspring from HFD-fed dams had increased body weight and adiposity, developing fatty liver, hyperinsulinaemia and insulin resistance at weaning. Interestingly, increasing prolactin levels in HFD-fed mothers improved mammary gland function and reduced visceral adiposity, ameliorated fatty liver and improved insulin sensitivity in offspring[153].

Thus, modification of the maternal diet has a high potential for childhood obesity reduction, by improving the maternal and fetal metabolic environment. In addition, there is also evidence to suggest that the benefit of these interventions may extend to the adult health of the offspring[48].

Transgenerational programming of obesity

During the past two decades, there has been a marked increase in the global prevalence of adult and childhood obesity[4]. Notably, the obesity phenotype has occurred in a relatively short period (one or two generations)[99]. Since the 1980s decade, Beach *et al.*[154] drove attention to the physiological response of the offspring across two or more generations, a term now called 'transgenerational programming'[155]. More recently, offspring from rats treated with dexamethasone during pregnancy presented retarded fetal growth, hypertension and glucose intolerance which, in turn, had effects on glucose homeostasis that persisted for two more generations[11,156].

In another study, maternal high-fat feeding caused a sex-specific insulin-resistant phenotype in second- and third-generation mice offspring[157]. In addition, Dunn & Bale[158] previously reported that maternal HFD exposure in mice results in an increase in body size and reduced insulin sensitivity, which persisted to the F2 generation via both maternal and paternal lineages. In mice, it has been shown that both male and female offspring present increased body weight and adiposity over generations exposed to multigenerational HFD feeding[74]. Thus, a vicious cycle develops, as females born to women with obesity may have an increased risk of obesity and give birth to subsequent generations with the same risks[99]. In contrast, the transmission of programming effects to subsequent generations perpetuates a cycle of obesity and metabolic disorders. However, the mechanisms responsible for these transgenerational effects remain to be elucidated.

White adipose tissue represents a prime target of metabolic programming induced by maternal obesity[45]. Perturbations to the perinatal nutrient supply may affect adipocyte development, conducing to persistent alterations in adipocyte number and physiology[82]. Indeed, in fetuses and neonates, adipocytes are sensitive to maternal factors. In humans, it is well characterised that an increase in the number of adipocytes occurs early in life, which is a determinant for fat mass in adulthood[37]. Conversely, in rodents, adipose tissue growth and adipogenesis mainly take place during the last week of gestation and accelerate throughout lactation[159]. Despite the evidence that adipogenesis occurs throughout life, maternal obesity at conception may predispose to adipose tissue development, resulting in higher white adipose tissue mass and hypertrophied adipocytes in children and adults[110].

Overnutrition (i.e. HFD feeding) during lactation and/or post-weaning periods leads to accelerated growth and alterations in adipogenesis and lipogenesis programming[160]. This correlates with an up-regulation of the key adipogenic factor PPARγ, characteristic of fat expansion in the offspring from mothers with obesity[95,100]. These observations agree with the 'adipose tissue expandability hypothesis', which proposes that insufficient precursor availability to enable increased adipogenesis, when challenged with a high-energy diet, limits adipocyte hyperplasia and hampers replacement of dead adipocytes. As a result, the adipose tissue of maternal obesity offspring has the impaired ability to maintain the progenitor pool. The premature differentiation of offspring progenitor cells limits the corresponding adipose tissue expandability, leading to adipocyte hypertrophy, a cause of hypoxia and inflammation, two major characteristics of type 2 diabetes mellitus[45].

Conclusions

Adipocytes play a critical role in whole-body energy homeostasis and endocrine regulation in all stages of life. Gestation and early postnatal life are critical plastic periods for programming

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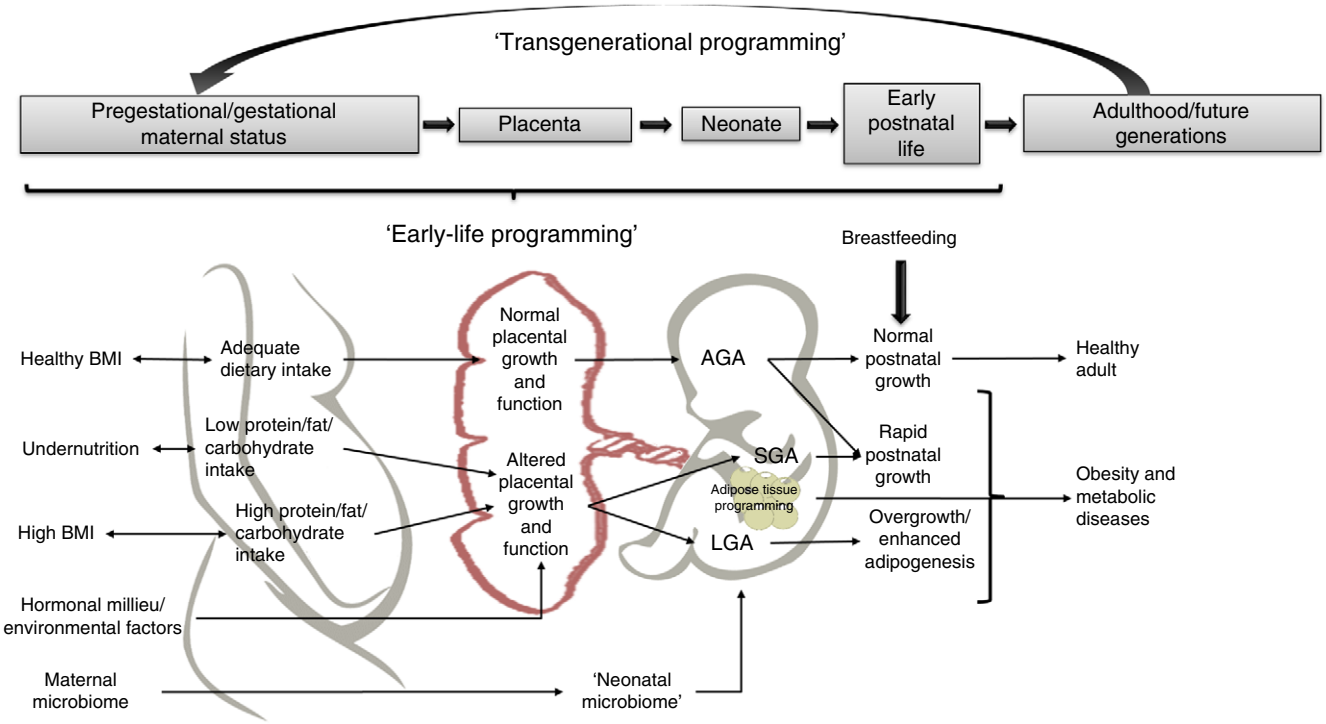


Fig. 2. Potential mechanisms linking early-life factors during pregnancy that may lead to obesity in children and adults. AGA, appropriate for gestational age; SGA, small for gestational age.

adipose tissue biology, as adipocyte development and physiology may be modelled by several maternal factors such as genetics, environmental influences, epigenetic changes, nutritional status, hormonal signalling and energy balance. This programming may lead to obesity and its co-morbidities in the progeny, with further transgenerational transmission and development of chronic diseases later in life (Fig. 2).

The complexity of adipose tissue results in numerous challenges for this study area. Therefore, the mechanisms by which adipose tissue development and physiology change in response to environmental demands are now being elucidated. Some of the questions in this topic that must be addressed that could greatly contribute to the DOHaD field are:

(a) How is placental development and physiology influencing fetal adiposity and how is the placenta programmed by maternal and/or paternal pregestational conditions, such as obesity or metabolic status?
(b) How is adipose tissue development and location programmed by specific macro- and micronutrient intake during gestation?
(c) Which molecular mechanisms and/or specific genes are involved in the epigenetic programming of fetal adiposity?
(d) What is the role of maternal gut and breast milk microbiota in adipose tissue programming of the offspring?
(e) How does breast milk composition change in response to maternal hormonal, nutritional and metabolic status, and how can these changes influence adipose tissue development in the neonate?
(f) Which are the precise mechanisms behind transgenerational programming of obesity in humans?

The potential impact of these findings for public health is vital, because pregnancy and early infancy represent critical windows of opportunity during which parents are most willing to adopt lifestyle changes, which, in turn, may have significant health implications across multiple generations.

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