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# Maternal Undernutrition and Fetal Developmental Programming of Obesity: The Glucocorticoid Connection

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**Abstract**

An adequate maternal nutrition during pregnancy is crucial for the health outcome of offspring in adulthood. Maternal undernutrition during critical periods of fetal development can program the fetus for metabolic syndrome (MetS) later in life, especially when postnatally challenged with a hypernutritive diet. Adipogenesis, which begins in utero and accelerates in neonatal life, is a major candidate for developmental programming. During fetal development, the hypothalamic–pituitary–adrenal (HPA) axis is extremely susceptible to programming, and the HPA tone is increased throughout life in undernourished conditions. As a consequence, an alteration in the expression and function of glucocorticoid (GC) receptors and of the major GC regulatory enzymes (11β-hydroxysteroid dehydrogenase 1 and -2) occurs. In this review, we will give insights into the role of maternoplacental adverse interactions under the specific context of maternal undernutrition, for later-in-life MetS development, with a special emphasis on the role of GCs.

**Keywords**

metabolic syndrome, maternal undernutrition, glucocorticoids, fetal developmental programming

## Introduction

Observations from epidemiological studies and animal models indicate that obesity and metabolic syndrome (MetS) depend not only on an interaction between genes and traditional adult risk factors, but also on the interplay between genes and the embryonic, fetal, and early postnatal environment.[1] Indeed, a U- or J-shaped relationship between birth weight and later-in-life obesity and hypertension has been proposed,[2-4] with an increased risk of obesity at both ends of the birth weight spectrum. This clearly highlights the importance of adequate nutrition during pregnancy for the later-in-life health outcomes of the offspring. Changes in macro- and/or micronutrient composition of the maternal diet during critical windows of fetal development (which are very plastic due to a very high rate of cell proliferation) can have pronounced effects on the placenta and fetus,[5] increasing the predisposition to MetS, most probably via epigenetic modification of genes involved in a number of key regulatory pathways.[5] Thus, MetS can be considered a developmental process that can be programmed by changes in the nutritional environment in early life. These nutritional programming effects may be either directly or indirectly mediated by endocrine changes in the mother.[1]

## Undernutrition and Fetal Development

In normal conditions, maternal dietary intake is adequate and is not reflected in infant's birth weight or growth over the first 6 months. Nausea and vomiting, which are common symptoms in early pregnancy, may alter food intake but the clinical consequences are poorly understood, and the conclusions of the studies are not consensual.[6-8]

The earliest studies relating early life undernutrition to later development of obesity resulted from epidemiological data from the Dutch "Hunger Winter" (a short-term famine in 1944-1945).[9,10] Maternal nutrient restriction during early gestation had no effect upon birth weight, although, as adults, these offspring exhibited a more atherogenic lipid profile and an increased risk of MetS compared to nonexposed people.[11] On the other hand, maternal nutrient restriction during mid-gestation, coincident with a phase of rapid placental growth, fetal growth, and tissue remodeling, had a slight impact upon birth weight and upon the risk of MetS.[12] Finally, maternal undernutrition during late gestation, coincident with a phase of rapid fetal development, had the greatest effect upon fetal

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growth, with shorter and thinner offspring, possessing smaller head circumferences. In middle age, similar to the offspring of early gestation maternal undernutrition, these group of individuals had increased susceptibility to develop impaired glucose tolerance and were predisposed to type 2 diabetes mellitus.[13] These pioneer observations suggested that perturbing the development of central endocrine regulatory systems during gestation may contribute to the later development of MetS and formed the basis of the "thrifty phenotype hypothesis."[14,15]

More recent studies have shown that Ramadan fasting affects both placental and fetal development. For instance, the relative risk of low birth weight was found to be 1.5 times higher in Iranian mothers on fasting at first trimester when compared to nonfasting mothers.[16] However, other studies showed that the ratio of placental-to-birth weight rose during the Ramadan in Saudi Arabia,[16,17] suggesting that the Ramadan lifestyle increases placental efficiency.[18] However, these results can be arguable, as the increase in the placenta size might be associated with a reduction in its efficiency since the placenta size increased with no alterations in the fetus weight. Of note, apparent contradictory conclusions in different studies may arise from differences in study design (including in particular the timing of sample collection in relation to the last meal), in seasonal and climatic conditions, and in the health, fitness, and activity levels of the study populations.

In another study (the Helsinki Birth Cohort), a link between hypertension in the offspring and the lifetime nutrition of the mother, as assessed by maternal height, was suggested. Interestingly enough, in people whose mothers were short (below 160 cm), the prevalence of hypertension increased progressively with decreasing placental area.[19] Short women have less visceral mass than tall women and have lower rates of amino acid synthesis in pregnancy.[19] It has been hypothesized that the effects of reduced availability of amino acids in the maternal circulation are exacerbated by restricted placental growth, which limits the transport of amino acids from the mother to the fetus. As such, expansion of the placental surface along its breadth may be one way in which a fetus may compensate for undernutrition. This may be beneficial in some circumstances, but if the compensation is inadequate and the fetus continues to be undernourished, the need to share its nutrients with an enlarged placenta may become an extra metabolic burden. As a result, a long-term cost of this fetal undernourishment is hypertension, possibly as a result of impaired development of low-priority organs such as the kidney, as mentioned earlier.[20]

Later, and as predicted by the thrifty phenotype hypothesis,[21] experimental studies in animals supported the notion that maternal undernutrition during critical periods of fetal development can program adipocyte metabolism and fat mass to give later rise to obesity, especially when the fetus is postnatally challenged with a hypernutritive diet.[22-24] Evidence from low birth weight sheep, which have a higher fat mass as neonates when compared with higher birth weight offspring,[25] shows an altered adipocyte function associated with an increased mRNA expression of several fat metabolism key regulatory genes such as uncoupling protein (UCP) 2 and peroxisome proliferator-activated receptor (PPAR) α. There is also evidence that a moderate (50%) or severe (70%) prenatal caloric restriction in rodents programmes this susceptibility,[26,27] although only after a postnatal dietary challenge.[28] Accordingly, other studies in rodents reported that protein (50%)[26] or vitamin (50%) restriction[29] increased body fat content in adult offspring, clearly demonstrating the adverse potential of maternal undernutrition to early program the adipogenesis in the offspring adulthood.

Moreover, several studies have shown that a protein-restricted diet during pregnancy in the F0-generation results in elevated blood pressure, endothelial dysfunction, insulin resistance, and adverse glucose homeostasis in the F1, F2, and even in the F3 generations. Interestingly enough, these effects were reversed by supplementing the diet with glycine or folic acid but not with alanine or urea.[30-32] Furthermore, hypomethylation of the hepatic PPAR-α and glucocorticoid receptor (GR) promoters was also prevented by supplementation of the protein-restricted diet with folic acid.[33] These results imply that transmission of a phenotype to the F1 and F2 generations and further to the F3 generation may involve preservation of levels of DNA methylation of specific genes and that 1-carbon metabolism plays a central role in the induction of an altered phenotype through epigenetic alterations.

Finally, the association between fetal growth restriction (FGR) and preeclampsia (in which FGR is also observed) and the postnatal development of obesity, which has been proven in human epidemiological studies and animal models,[14] also supports a close link between fetal undernutrition and later-in-life obesity. Indeed, an adverse in utero development precedes both these pathologies, with an abnormal or insufficient placentation being the probable underlying cause. Interestingly, this is accompanied by a downregulation of key placental nutrient transporters (eg, amino acid transporters).[18] It has been hypothesized that the placenta is a nutrient sensor and that maternal malnutrition and/or placental insufficiency results in downregulation of placental nutrient transporters, resulting in fetal undernutrition with a consequent decrease in fetal growth.[34]

Two major factors have been proposed to underlie early life programming of obesity and MetS by maternal undernutrition: fetal undernutrition itself[35] and overexposure of the fetus to glucocorticoids (GCs).[36,37] The latter can be a consequence of an alteration in expression or function of GRs, of GCs major regulatory enzymes, or of the precocious activation of the hypothalamic–pituitary–adrenal (HPA) axis. Of note, these 2 hypothetical factors are probably overlapping as, for example, in animal models, GCs can alter maternal food intake, and conversely, maternal undernutrition increases maternal GC secretion, reduces placental 11β-hydroxysteroid dehydrogenase (11β-HSD) 2 activity (as discussed subsequently), and thus alters fetal GC exposure. These alterations can be either perpetuated through generations or reverted by supplementation with specific amino acids or vitamins that alter the methylation status of the above-referred specific regulatory genes. We will next focus mainly upon the putative influence of maternal

undernutrition upon GC levels (1) directly, by the activation of the HPA axis, and (2) indirectly, by alteration in expression and function of GR and GC major regulatory enzymes.

## Hypothalamic–Pituitary–AdrenalAxis, GC Secretion, and Effects on Adipose Tissue

The synthesis of GCs, which occurs in the zona fasciculata/reticularis of the adrenal cortex, is regulated by the activity of the HPA axis in a classical negative feedback loop. In brief, stress conditions lead to an augmented production and release of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP) from the paraventricular nucleus. These hypophysiotropic hormones are released into the portal blood system and act synergistically via their receptors (CRH via the CRH-R1 and AVP via the V1b receptor) on cells of the anterior pituitary to stimulate adrenocorticotropic hormone expression and release, which in turn, via melanocortin-2 receptors, increase GC production at the adrenals. Subsequently, the increased levels of circulating GCs induce a negative feedback to inhibit HPA axis activity, thus preventing excessive production of stress hormones.[38]

The HPA axis is extremely susceptible to fetal programming. Alterations in the maternal nutritional status, specifically maternal starvation, which, from the point of view of this review will be considered as early insults and forms of stress to the fetus, are likely to reprogram HPA axis development resulting in an increased HPA tone through life.[37] Of importance in this context, the HPA axis is responsible for the secretion of the major obesogenic hormones, the GCs. Glucocorticoids are key mediators of stress responses, being thus essential for life, and play a key role during fetal development. In fact, during late gestation, GCs stimulate surfactant production by the lung, promoting fetal growth and organ maturation in order to prepare the fetus for extrauterine life.[39,40] However, fetal overexposure to GCs can be harmful as GCs cause a shift from cell proliferation to differentiation, thus altering fetal organ growth and maturation patterns, which can result in adverse consequences later in life, as reviewed elsewhere.[41]

Glucocorticoids are major regulators of distinct aspects of adipocyte biology and fat deposition, being involved not only in the promotion of energy mobilization (eg, glucose, amino acids, fatty acids, and glycerol) but also in stimulation of liver gluconeogenesis. Although GCs have a lipolytic nature, their effect upon adipose tissue metabolism is conflicting because individuals with elevated GCs levels, as observed in patients with Cushing syndrome (CS), present an associated central adiposity. Indeed, excessive levels of these hormones in adipocytes are associated with metabolic disorders, including central obesity, insulin resistance, and dyslipidemia.[42] Evidence from rodents demonstrates that central dexamethasone infusion resulted in a marked increase in food intake and body weight. Also, a state of hyperinsulinemia, hyperleptinemia, and hypertriglyceridemia was observed, accompanied by a pronounced decrease in the expression of UCP-1 and -3 in brown adipose tissue and of UCP3 in muscle. Such effects are centrally stimulated, mainly via an intensification of hypothalamic neuropeptide Y levels, which results in an activation of the parasympathetic nervous system.[43,44] On the other hand, GCs also directly affects adipogenesis at the tissue level, as preadipocytes are stimulated to differentiate into mature adipocytes by both cortisol and dexamethasone in a dose-dependent fashion, as reviewed elsewhere.[45] Altogether, GCs have direct and indirect adipogenic effects, because they have the ability to alter insulin and leptin sensitivity and, as such, to influence food intake and also because they regulate adipogenesis locally at adipocyte level.

Besides affecting fetal adipose tissue, GC also affects other processes during fetal development. Namely, GCs are important for maturation of most regions of the developing brain[46,47] and for neuronal survival.[48] However, prenatal GC administration reduces sheep brain weight at birth, delaying maturation of neurons, myelination, glia, and vasculature,[49] and causes a dose-dependent degeneration of hippocampal neurons and a reduced hippocampal volume in rhesus monkeys.[50] During midgestation, there is plentiful 11β-HSD-2 in the CNS, which presumably ''protects'' vulnerable developing cells from premature GC action (see subsequently). However, at the end of midgestation, expression of 11β-HSD-2 is dramatically switched off in the rat, mouse, and human brain, coincident with the terminal stage of neurogenesis.[49] The hippocampus being one of the major regulators of the HPA axis, this persistent exposure to excessive plasma GC leads to increased HPA tone through life, as previously stated, and consequently exacerbates hypertension and hyperglycemia.[51] Furthermore, at the heart level, prenatal GC exposure alters the development of sympathetic processes, increases adenyl cyclase activity, alters metabolic key regulators (eg, the glucose transporter 1, akt/protein kinase B and PPARγ),[49] and, mediated by an interaction with reactive oxygen species, is associated with alterations in endothelial function and coronary vascular smooth muscle cell proliferation.[52] These changes in coronary physiology, known to be associated with the development of atherosclerosis, may provide an important link between an adverse intrauterine environment and a later increased risk of cardiovascular disease.[52] Moreover, observations in rats have concluded that in utero GC exposure (through maternal GC administration) reduces fetal skeletal muscle mass in rats independent of effects on maternal nutrition.[53] Also, prenatal dexamethasone treatment in rats resulted in changes in the expression of CYP3A1 as well as in the histology of fetal livers[54] and induced glucose intolerance later in life in the offspring, associated with an increased hepatic expression of GR and phosphoenolpyruvate carboxykinase.[55] Finally, maternal undernutrition leading to increased GC levels originated an impaired pancreatic β-cell development, and consequently reduced insulin levels as well as glucose intolerance in adulthood.[56-58] Altogether, it can be concluded that GC exposure affects fetal development in several different tissues and that distinct mechanisms appear to contribute to the effect of GC in fetal programming. However, we will next focus on the effects of GC upon adipogenesis.

## Role of GCs and Adipose Tissue in MetS Programming

Adipogenesis, which begins in utero and accelerates in neonatal life, is a major candidate for developmental programming. It is uncertain how maternal influences on fetal adipogenesis may determine the timing of the "adiposity rebound," but the programming of adipocyte morphology and metabolism during fetal development is certain. Because the diagnostic features of MetS, such as insulin resistance, dyslipidemia, hypertension, and visceral obesity, are shared by CS, which results from endogenous or exogenous hypercortisolism, it was proposed that cortisol contributes to the pathogenesis of both states.[59] On the other hand, MetS comes along with chronic low-grade inflammation in adipose tissue with concomitant increased levels of 11β-HSD1. Thus, it has been suggested that inhibiting cortisol action, either directly or indirectly modulating GC regulatory enzymes, could provide a novel therapeutic approach for MetS.[59]

In fact, in animal models of fetal programming and FGR involving maternal low-protein diet (which causes a reduction in birth weight and leads to MetS in the offspring), an increase in maternal and fetal GC levels was found[60] together with a decrease in placental 11β-HSD2 activity and/or expression.[61] The strong similarities between the phenotypes associated with antenatal GC exposure and maternal nutritional restriction have prompted consideration that undernutrition may act as a stressor that alters the endocrine cross-talk between mother and fetus. This has led to the hypothesis that undernutrition promotes overexposure of the fetal tissues to maternal GCs, which drives tissue remodeling and the development of the programmed phenotype.[61] In fact, GC administration reduces fetal growth and stably alters gene expression in a manner that favors increased production and storage of energy substrates, with increased risk of hyperlipidemia, hyperglycemia, and hypertension.[62,63] Moreover, human fetal-blood cortisol levels are increased in FGR, implicating endogenous cortisol in this condition.[64] Also, dexamethasone treatment of pregnant rats reduces birth weight and elevates blood pressure in adult offspring,[65] pointing to a clear involvement of GCs in programming of MetS during maternal undernutrition. Of note, studies in the sheep have shown that applying GC directly to the fetus, contrary to administration of GC to pregnant animals, does not result in FGR. This is compatible with the possibility that the placenta mediates the effects of GC on fetal growth.[34] Interestingly enough, observations by our group demonstrated that dexamethasone reduces the cellular uptake of glucose in a human first-trimester trophoblast cell line (Correia-Branco et al, unpublished results), which could also contribute to the reduced fetal growth seen after GC exposure.

## Molecular Regulators of GC Activity in Maternal Undernutrition

The effects of GCs are mediated by activation of intracellular GR (gene name NR3C1), which are expressed in placenta and most fetal tissues from mid-gestation onward.[66] The receptor–ligand complex then translocate into the nucleus and then targets promoter elements of a plethora of genes involved in various physiological processes, including energy metabolism and inflammation. Glucocorticoid receptor binds with high affinity only to reduced forms of GCs.[37] Interestingly, 2 microsomal enzymes collectively referred to as the 11β-HSD system catalyze the interconversion of active GCs (cortisol in humans and corticosterone in rodents) and physiologically inactive 11-keto forms (cortisone and 11-dehydrocorticosterone, respectively). The GC inactivation process is catalyzed by 11β-HSD2, and the reverse reaction is catalyzed by 11β-HSD1.[37] Therefore, this consists in an additional regulatory step prior to GC action.[37]

11β-Hydroxysteroid dehydrogenase 2 is highly expressed at the interface between maternal and fetal circulations, that is, at the syncytiotrophoblast in humans[67] and in the labyrinthine zone in rodents.[68] Thus, the placenta forms a functional, although not complete, "barrier" to maternal GCs due to high placental 11β-HSD2 expression and activity. Accordingly, inhibition of 11β-HSD2, by impairment of either the expression or activity of this enzyme, is expected to lead to an increase in maternal-to-fetal transplacental transport of active GCs.[61,69-72]

### *Glucocorticoid Receptor*

Obesity has been associated with reduced sensitivity to GC feedback,[73,74] an effect thought to be mediated via altered sensitivity of GR. In fact, GR messenger RNA (mRNA) levels increase with fat mass and increased GR expression has been observed in patients with visceral obesity. Thus, genetic and environmental variations in GR density in metabolic tissues may underlie MetS.

Maternal nutrient restriction during pregnancy in sheep results in increased obesity and adipose tissue GR expression in the fetus.[75,76] Moreover, there is now evidence that exposure of human fetuses to high levels of GCs—whether from exogenous or endogenous origins—can permanently affect GR expression. For instance, inhibition or deficiency of placental 11β-HSD2 has been shown to reduce hippocampal GR expression,[68] the site of central negative feedback, with an expected HPA axis overactivation.[77] Additionally, administration of dexamethasone to pregnant rats increases basal corticosterone levels, and this is associated with a reduction in hippocampal GR expression[68] as well as with an increase in GR expression in visceral adipose tissue and alterations in fat metabolism which may contribute to insulin resistance of the offspring.[78]

Many GR binding regions are located in or nearby genes involved in triacylglycerol (TG) synthesis (Scd-1, 2, 3, GPAT3, GPAT4, Agpat2, and Lpin1), lipolysis (Lipe and Mgll), lipid transport (Cd36, Lrp-1, Vldlr, and Slc27a2), and storage (S3-12). The majority of these genes were induced in transgenic mice that have constant elevated plasma GC levels and in mice treated with GC, which was associated with increased TG synthesis and lipolysis concomitantly in inguinal fat, indicating

that a GC-controlled gene network is involved in the regulation of TG homeostasis. A recent study compiled the GR target genes involved in the "metainflammation" described so far, and several genes related to MetS (eg, HSD11B1, IGF1, IGFBP1, INSR, ISR1, MGMT, MYC, NOTCH4, PCK1, PIK3R1, PPARA, PTPN22, and SERPINE1), cholesterol metabolism, inflammatory mediators, and inflammatory cytokines/cytokine receptors (eg, TNF-α, ICAM1, NFkB, JUN, IFNB1, IL6, IL7R, IL8, and IL11) were found. Interestingly enough, several target genes were found to provide GC feedback regulation.[79]

Thus, in summary, maternal undernutrition may decrease GR levels in fetal hippocampus, with a subsequent overactivation of the HPA axis. This latter will, therefore, affect the adiposity in the fetus. On the other hand, fetal increased GC levels may directly alter GR expression in insulin-target tissues such as adipose tissue, with a consequent alteration in the regulation of lipogenesis and lipolysis and with a concomitant unset upon MetS.

### *11β-Hydroxysteroid dehydrogenase 1*

Converging lines of evidence from epidemiological studies and animal models provide evidence that 11β-HSD1 reamplifies local tissue GC levels, therefore constituting a prime etiological factor in obesity and MetS.

More specifically, transgenic mice that selectively overexpress adipose tissue 11β-HSD1 have increased adipose tissue levels of corticosterone, develop visceral obesity, and are glucose intolerant.[80] On the contrary, homozygous 11β-HSD1$^{-/-}$ knockout mice are protected from features of MetS and obesity, that is, they are protected from hyperglycemia and display a cardioprotective serum lipid profile.[81] Moreover, this mice strain express: (1) lower levels of proobesogenic markers such as resistin and TNF-α and (2) higher levels of antiobesogenic markers such as PPAR-γ, adiponectin, and UCP-2 mRNA in adipose tissue, indicating increased insulin sensitivity. Importantly, altered expression of adipocyte 11β-HSD1 has been reported in response to maternal undernutrition. In fact, adipocytes of prenatally nutrient-restricted lambs show increased expression of 11β-HSD1, which could lead to augmented cortisol exposure and proliferation of adipocytes.[82] More recently, early nutrient restriction in sheep has been reported to increase expression of both 11β-HSD1 and GR.[75] As such, maternal nutrient restriction can alter 11β-HSD1 expression in the fetus, programming later obesity. 11β-Hydroxysteroid dehydrogenase 1 has thus emerged as a major potential drug target for the treatment of obesity and its associated medical conditions.

### *11β-Hydroxysteroid dehydrogenase 2*

11β-Hydroxysteroid dehydrogenase 2 is expected to display an antiobesogenic nature. In agreement with this, 11β-HSD2 expression and/or activity has been shown to be attenuated in FGR placentas[34] and patients with visceral obesity.[83] In experimental animal models, chronic maternal undernutrition and stress during pregnancy have been associated with a decreased

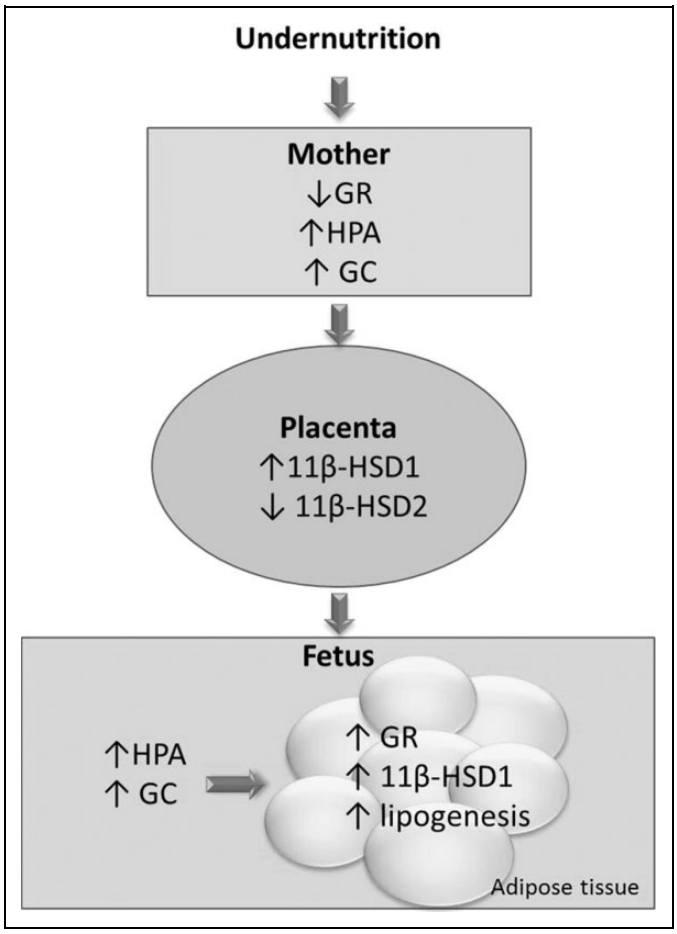


**Figure 1.** Simplified schematic diagrams illustrating the hypothesis suggested in this review. Maternal undernutrition induces maternal increase in HPA activation and GC levels along with a reduction in GR expression. This will have consequences upon the placenta, with an increased expression of 11β-HSD1 associated with a reduction in 11β-HSD2. As a result, the fetus will be exposed to increased GC levels, either by maternal origin or by increased activation of fetal HPA. This will have effects upon fetal adiposity, with an increased expression of GR and 11β-HSD1 in the developing adipose tissue and an increase in fetal lipogenesis. HPA indicates hypothalamic–pituitary–adrenal; GC, glucocorticoid; GR, glucocorticoid receptor; 11β-HSD, 11β-hydroxysteroid dehydrogenase.

expression of placental 11β-HSD2 or with a reduction in the capacity of the placenta to upregulate 11β-HSD2 activity.[83] Interestingly enough, in programming animal models involving maternal low-protein diet (which also reduces birth weight and leads to MetS in the offspring), an increase in maternal and fetal GC levels was found[60] together with a decrease in placental 11β-HSD2 activity and/or expression.[61] Nevertheless, whether the restrained expression of 11β-HSD2 is a direct result of the diet on the enzyme function or an indirect consequence of the altered maternal GC levels is still unknown.

## Conclusion

Overall, GCs appear to be involved in the programming of MetS and obesity during in utero life. Maternal undernutrition

leads to an augmented expression of GC in the mother and GC overexposure of the fetus by the following putative ways: (1) direct activation of maternal and fetal HPA, (2) increased fetal adipose tissue expression of GR, (3) augmented fetal and placental expression of 11β-HSD1, and (4) reduction in fetal 11β-HSD2 expression (Figure 1).

In conclusion, GC system unbalance can be considered a major etiological factor contributing to fetal adipogenesis and to the later-in-life development of obesity and MetS in response to maternal undernutrition. As such, the study of the mechanisms underlying GC system unbalance is of major importance to understand the etiology of fetal adipogenesis and the later-in-life development of obesity and MetS.

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