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REVIEW

Mechanisms of developmental programming of the metabolic syndrome and related disorders

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Abstract

There is consistent epidemiological evidence linking low birth weight, preterm birth and adverse fetal growth to an elevated risk of the metabolic syndrome (obesity, raised blood pressure, raised serum triglycerides, lowered serum high-density lipoprotein cholesterol and impaired glucose tolerance or insulin resistance) and related disorders. This "fetal or developmental origins/programming of disease" concept is now well accepted but the "programming" mechanisms remain poorly understood. We reviewed the major evidence, implications and limitations of current hypotheses in interpreting developmental programming and discuss future research directions. Major current hypotheses to interpret developmental programming include: (1) thrifty phenotype; (2) postnatal accelerated or catch-up growth; (3) glucocorticoid effects; (4) epigenetic changes; (5) oxidative stress; (6) prenatal hypoxia; (7) placental dysfunction; and (8) reduced stem cell number. Some hypothetical mechanisms (2, 4 and 8) could be driven by other upstream "driver" mechanisms. There is a lack of animal studies addressing multiple mechanisms simultaneously and a lack of strong evidence linking clinical outcomes to biomarkers of the proposed programming mechanisms in humans. There are needs for (1) experimental studies addressing multiple hypothetical mechanisms simultaneously; and (2) prospective pregnancy cohort studies linking biomarkers of the proposed mechanisms to clinical outcomes or surrogate biomarker endpoints. A better understanding of the programming mechanisms is a prerequisite for developing early life interventions to arrest the increasing epidemic of the metabolic syndrome, type 2 diabetes and other related disorders.

Key words: Fetal origins; Developmental programming mechanisms; Metabolic syndrome; Insulin resistance; Type 2 diabetes

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INTRODUCTION

The metabolic syndrome is commonly defined as a combination of at least three of the following five con-

ditions: obesity, elevated blood pressure, elevated serum triglycerides, low serum high-density lipoprotein (HDL) cholesterol and impaired glucose tolerance or insulin resistance[1]. The clustering of these risk factors predisposes an individual to non-insulin-dependent (type 2) diabetes, cardiovascular morbidity and mortality. There is general consensus regarding the five components of the syndrome but definitions differ regarding cutoffs and mandatory criteria. Recently, central obesity [waist circumference > 102 cm in males or > 88 cm in females or body mass index (BMI) > 30] was proposed as a mandatory component by the International Diabetes Federation[2].

Epidemiological and experimental evidence suggest an association between an adverse prenatal environment and the risk of developing the metabolic syndrome and related disorders. This "fetal origins of disease" hypothesis was first proposed by Barker and Hales' group to explain the associations between low birth weight (LBW < 2500 grams) and increased risk of impaired glucose tolerance and cardiovascular disease in retrospective cohort studies[3-5]. Subsequent epidemiological studies in different populations largely confirmed this "fetal origins" phenomenon[3-8]. In recent years, the term "fetal origins/programming" has been replaced by "developmental origins/programming" to accommodate the increasingly accepted concept that "programming" may continue in the early postnatal period.

A number of hypotheses have been proposed to interpret developmental programming[9-14] but none have received unanimous recognition. It is now worth reflecting on what is known about the mechanisms of developmental programming after decades of research. We critically reviewed the key evidence, implications and limitations of current hypotheses to interpret developmental programming of the metabolic syndrome and discuss the directions for future research. The evidence acquisition was based on a literature review based on a PubMed search of publications between January 1970 and February 2010.

MAJOR HYPOTHESES

We use the term "major hypotheses" to refer to those supported by substantial epidemiological and experimental evidence. Two competing major hypotheses have been proposed: "thrifty phenotype" and "postnatal accelerated growth".

Thrifty phenotype

Rationale: Hales and Barker proposed the thrifty phenotype hypothesis (Figure 1)[11,12]. The hypothesis suggests that fetal and early postnatal malnutrition may induce poor development of pancreatic β-cell mass. Malnutrition may have a selective impact on the growth of different organs with protection of the most vital (e.g. the brain). Because altered growth during critical periods permanently changes the structure and functional capacity of pancreatic β-cell mass, such changes may "program" the metabolic system

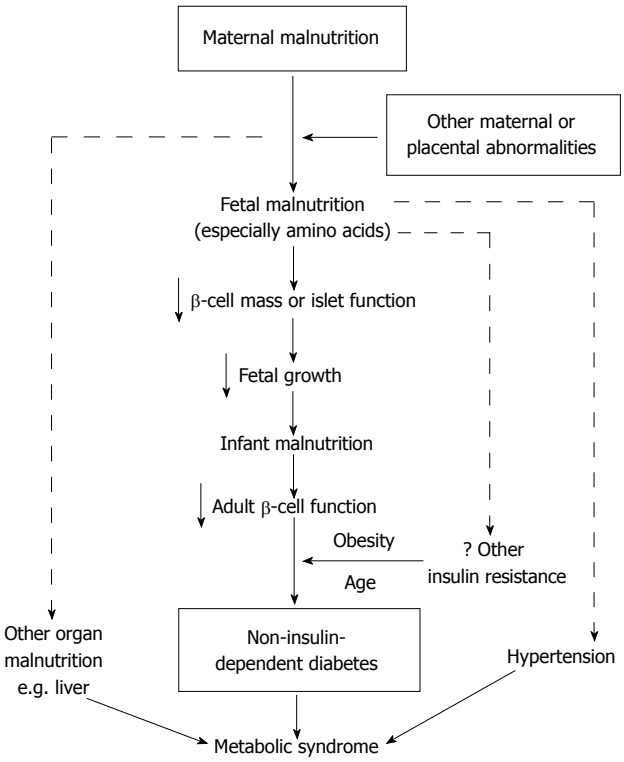

Figure 1 The thrifty phenotype hypothesis (reproduced with permission, Hales and Barker[12]).

which increases the fetus' chance of survival in poor nutritional environments but results in difficulty in coping with nutritional abundance later in life. The development of the metabolic syndrome following malnutrition in early life may depend on the superimposition of other postnatal risk factors, notably physical inactivity and obesity.

Epidemiological evidence: Barker and colleagues observed in 1986 that the geographical distribution of heart disease in the United Kingdom was closely related to a person's place of birth[15], suggesting that early life events could cause permanent changes in physiology predisposing to chronic heart disease. LBW has been strongly linked with impaired glucose tolerance and type 2 diabetes in adulthood[3-5,16-18]. Reduced fetal growth was related to increased plasma concentrations of 32-33 split proinsulin, a sign of beta-cell dysfunction[19-21], and was linked to high blood pressure[22,23]. Children small in birth size may predispose to metabolic abnormalities upon exposure to postnatal environmental risk factors such as low physical activity and/or high-energy intake[24]. Prenatal exposure to famine during the Dutch Hunger Winter of 1944-1945 was associated with impaired glucose tolerance and insulin secretion in adulthood[25,26]. The Pune Maternal Nutrition Study correlated prenatal specific micronutrient (vitamin B_{12}) deficiency with increased insulin resistance in childhood[27]. Changes resulting from fetal and early postnatal malnutrition include: (1) metabolic adaptations in hepatic enzymes[28], lipoprotein profiles[29] and clotting factors[30]; (2) anatomical adaptations that affect end-organ glucose uptake[31] and renal solute metabolism[32]; and (3) endocrine

adaptations that affect the hypothalamic-pituitary-adrenal (HPA) axis[33], insulin signaling[34] and leptin levels[35]. These changes could collectively lead to the metabolic syndrome and related disorders[36].

Experimental evidence: In animal models, fetal malnutrition has been associated with marked structural and physiological alterations[37-39]. Gestational calorie restriction and protein deprivation in rats led to hypertension in adult offspring[40-42] and to altered glucose metabolism in sheep[43,44]. Malnutrition-associated changes in fetal leptin levels may alter the programming of appetite and eating behaviors leading to an increased risk of cardiovascular and metabolic diseases[45-48]. The pattern of dietary response of inbred mouse strains was similar to that expected under the thrifty phenotype hypothesis[49]. Permanent reductions in pancreatic cells and insulin secretion have been observed in protein-malnourished fetuses[50].

Implications and limitations: The thrifty phenotype is the most widely accepted hypothesis to interpret developmental programming. The hypothesis emphasizes the etiological role of poor fetal and early postnatal nutrition and implicitly advocates promoting fetal and infant nutrition and growth[51]. It may well explain the increasing prevalence of obesity and type 2 diabetes in India and South Asian countries where malnutrition was previously common but has become less so in recent decades[52]. However, in virtually all human studies, maternal and fetal nutritional status, as determined either directly by specific nutrient biomarkers or indirectly by weight gain during pregnancy, were not available for linkage to clinical outcomes. The hypothesis does not match the trends of increasing birth weights and declining LBW rates in many countries in recent decades[53-55], raising concerns as to whether poor fetal nutrition or "thrifty phenotype" is a major driver of developmental programming. Furthermore, poor fetal growth is a mere proxy for various perinatal insults. It is plausible that adverse insults may drive both poor fetal growth and developmental programming.

"Postnatal accelerated growth" or "catch-up growth" hypothesis

Rationale: The "postnatal accelerated growth" hypothesis was proposed by Drs. Singhal and Lucas to explain the association between faster early postnatal growth and surrogate endpoints in childhood and adolescence indicative of metabolic and cardiovascular risks based on follow-ups of preterm infants in two early neonatal feeding/nutritional intervention trials[13,14]. Increased infant growth rate by a nutrient enriched diet, even for only a few weeks postnatally, was associated with long-term adverse metabolic effects[6-8,56]. Fasting concentrations of 32-33 split proinsulin (a marker of insulin resistance) in adolescents born preterm were significantly elevated among those who had received a nutrient-enriched diet in early postnatal life vs. placebo[7]. The authors concluded that early postnatal accelerated growth rather than prematurity *per se* may be the culprit in programming insulin resistance and related disorders[14].

Cianfarani proposed a similar "catch-up growth" hypothesis[9]. At birth, infants with intrauterine growth retardation (IUGR) have low concentrations of insulin, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein (IGFBP)-3; and high concentrations of growth hormone, IGFBP-1 and IGFBP-2. Normalization of these hormones occurs during the first trimester of postnatal life[57,58]. During this early postnatal catch-up growth period when suddenly exposed to increased concentrations of insulin and IGF-1, tissues chronically depleted of these two hormones during fetal life may counteract the hike by developing insulin resistance as a metabolic defense against developing hypoglycemia[9]. Therefore, IUGR infants who show early and complete growth recovery could be at higher risk for the occurrence of the metabolic syndrome in adulthood.

Dr. Gluckman proposed another similar hypothesis, the "predictive adaptive response"[10]. Based on the "predicted" postnatal environment, the fetus would make adaptations in utero or in the early postnatal period[10]. IUGR fetuses would thus predict a poor postnatal nutritional environment. When mismatch occurred between predicted and actual, disease would manifest[10,59].

Epidemiologic evidence: Early childhood growth acceleration has been associated with later insulin resistance[60], obesity[61] and cardiovascular disease[8]. In low birth weight infants, early growth acceleration has been associated with metabolic disturbances including dyslipidemia and elevated concentrations of insulin and IGF-1[9,62,63]. IUGR infants often experience compensatory accelerated growth after a period of poor fetal nutrition followed by the removal of such nutritional deficiency postnatally[64]. The most rapid growth occurs in early infancy[65] in the first few weeks after birth[66,67]. Factors promoting neonatal growth such as enhanced neonatal nutrition could permanently affect or program long-term health[68]. Such accelerated growth may have adverse consequences later in life[64], increase the propensity to cardiovascular disease[69] and its risk factors such as insulin resistance[70], obesity[65] and higher blood pressure[71]. Patients with impaired glucose tolerance or diabetes typically had a low BMI in infancy, an early adiposity rebound in childhood and an accelerated increase in BMI until adulthood[72].

Experimental evidence: In rats, accelerated early postnatal growth impaired glucose tolerance and shortened the lifespan[73]. Small neonatal rats temporarily overfed during the brief suckling period had permanent elevations in plasma insulin and cholesterol levels in adulthood[74]. Postnatal accelerated growth can adversely affect glucose tolerance in rats[75]. Even in rats without IUGR, overfeeding during the brief suckling period permanently increased later plasma insulin and cholesterol concentrations[76,77] with the propensity to obesity, high blood pressure and diabetes[53,77].

Implications and limitations: An important implication of the "postnatal accelerated growth" or "catch-up growth" hypothesis is that it questions the current practice of promoting postnatal catch-up growth of small babies[14]. Enhancing infant growth rate by a nutrient-enriched diet may actually do more harm than good in the long run. However, this hypothesis has been well tested only in preterm infants in Dr. Lucas's studies. It remains unclear whether the findings hold for catch-up growth in IUGR infants born at term. The increasing birth weights in most countries in recent decades[54,78-80] indicate that there are unlikely substantial increases in the incidence of postnatal catch-up growth. Consequently, it appears difficult to explain the substantial rise in the incidence of the metabolic syndrome. Also, the hypothesis does not match the epidemiological evidence of an elevated risk of the metabolic syndrome among macrosomic infants who often show catch-down rather than catch-up growth during the early postnatal period.

MINOR HYPOTHESES

We use the term "minor hypotheses" to refer to those supported by insufficient research data, especially in humans.

Glucocorticoids programming

A product of the activation of the HPA axis, glucocorticoids have potent effects on tissue development especially the maturation of organs such as the lung[81]. One outcome of fetal malnutrition is the exposure of the fetus to excess glucocorticoids which may restrict fetal growth and program the cardiovascular, endocrine and metabolic systems[82]. Normally, fetal glucocorticoid levels are much lower than maternal levels due to the placental barrier[83,84] - the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) catalyzes glucocorticoids (cortisol and corticosterone) into inert forms (cortisone, 11-dehydro corticosterone)[80,85]. However, synthetic glucocorticoids (betamethasone, dexamethasone) commonly administered to pregnant women at risk of preterm delivery to reduce neonatal pulmonary, renal and cerebral morbidities[86], are poor substrates of 11β-HSD2. Prenatal glucocorticoid overexposure through external sources or inhibition of placental 11β-HSD-2 may induce fetal HPA axis dysfunction - a potential link between adverse fetal environment and insulin resistance and hypertension in adulthood[87].

There is strong evidence of glucocorticoid programming in animal models. Many studies have reported decreased birth weights and abnormal levels of plasma HPA-axis hormones in rats prenatally exposed to synthetic glucocorticoids or inhibition of 11β-HSD2 with increased blood pressures and glucose intolerance in adulthood[87-89]. Hypertension in rats whose mothers were fed a low-protein diet during pregnancy was preventable by chemical blockade of maternal glucocorticoid synthesis[90], suggesting that the link between maternal protein deprivation and adult-onset hypertension may be mediated by maternal glucocorticoids. However, there is weak and inconsistent evidence regarding antenatal exposure to synthetic glucocorticoids and components of the metabolic syndrome in humans. Studies have reported no change, slight increase or decrease in blood pressure[91-94]. A Cochrane meta-analysis showed no differences in adult blood pressure[95]. In contrast, a recent follow-up study of 534 adults whose mothers had participated in a randomized controlled trial reported increased insulin resistance associated with antenatal betamethasone treatment[93]. LBW adults had much higher urinary glucocorticoid[96] and plasma cortisol concentrations[97] and showed greater responsiveness to adrenocorticotropic hormone[98,99]. Prenatal glucocorticoids may be the link between LBW and increased risk of glucose intolerance and hypertension[87]. Elevated blood pressure after antenatal exposure to glucocorticoids may result from altered renal renin-angiotensin system development[100] or from epigenetic changes affecting the expression of specific transcription factors, especially the glucocorticoid receptor[87].

However, there is a lack of strong evidence of glucocorticoid programming in humans. It remains unknown whether glucocorticoids drive both IUGR and the programming of metabolic syndrome components as observed in animal models.

Epigenetic programming

Experimentally, transmission to the next generation of a "programmed" phenotype has been demonstrated for birth weight, metabolic dysfunction[101-103], blood pressure and vascular dysfunction[104]. Wild type mice born to hypertensive heterozygous nitric oxide synthase-3 knockout mice displayed hypertension and vascular dysfunction[104]. Such transmission can be attributed to the fact that the programmed mother provided a deprived intrauterine environment, thus perpetuating the cycle of fetal (mal) adaptations. An alternate possibility is that epigenetic modification of the germline by stable DNA methylation or histone acetylation transmitted the prenatal experience of one generation to future generations.

Many candidate and confirmed players able to induce developmental programming can modify gene methylation. For example, Rees showed hypermethylation in the fetal liver of low protein fed dams[105]. Peroxisomal proliferator-activated receptor (PPAR) alpha and glucocorticoid receptor genes were hypomethylated and their expression increased in the liver of the offspring of protein-restricted rats[106]. Reactive oxygen species can modify methylation leading to changes in gene transcription and expression[107]. However, there are relatively little data demonstrating epigenetic changes after adverse perinatal conditions in genes closely implicated in cardiovascular and metabolic disorders. Bogdarina reported modifications in the methylation status of the angiotensin Ⅱ AT1b receptor gene in the adrenal gland of the offspring of low-protein fed dams[108]. Neonatal overfeeding in rats led to permanent dysregulation of the

central circuitry of food intake inhibition with resistance to signals triggered by insulin and leptin[109-111]. Circulating leptin and insulin stimulate the expression of the main anorexigenic neurohormone - proopiomelanocortin (POMC) while inhibiting the orexigenic neuropeptide Y[112,113]. Plagemann recently demonstrated hypermethylation of the hypothalamic POMC gene promoter region in neonatal overfeeding animals within two specific protein-1 (Sp-1) binding sequences. This led to blunted POMC expression despite hyperleptinemia and hyperinsulinemia and demonstrated that a nutritionally acquired alteration of the methylation pattern could modify the set point of a gene promoter critical for body weight regulation[114].

The availability of methyl donor micronutrients may affect epigenetic programming. Dietary protein restriction in pregnancy induced and folic acid supplementation prevented epigenetic modifications of hepatic glucocorticoid receptor gene expression in rat offspring[106]. Folate supplementation of low-protein fed dams prevented elevation of blood pressure in adult offspring[115]. Restricting the supply of vitamin B_{12}, folate and methionine even within normal physiological ranges during the periconceptional period was associated with widespread epigenetic alternations, insulin resistance and elevated blood pressure in sheep[116]. In contrast, maternal high folate status in pregnancy was associated with *increased* insulin resistance in children[27], indicating the need for caution in applying results from animal models to humans. Dietary methyl supplementation with folic acid and B_{12} may have unintended deleterious consequences on epigenetic regulation[117]. More human data are needed in this nascent research area.

It should be pointed out that epigenetic programming is a physiological process in normal fetal development; the epigenetic changes dictate cell differentiation. The question is, are some epigenetic changes "pathological" secondary to certain perinatal insults? There is a lack of human data linking perinatal "programming" insults to developmental epigenetic changes and later risk of the metabolic syndrome and related disorders. Improved understanding of epigenetic changes may be helpful in designing interventions to prevent or possibly reverse adverse programming.

Oxidative stress programming

Because many known or suspected causes of or conditions associated with adverse fetal growth or preterm birth have been associated with oxidative stress, it is plausible that oxidative stress may be the underlying common link to elevated risks of the metabolic syndrome[118]. Oxidative stress programming may act directly through modulation of gene expression (perhaps epigenetic) or indirectly *via* the effects of certain oxidized molecules. Experimental investigations have well demonstrated the role of redox balance in modulating gene expression[119,120]. There is considerable experimental evidence indicating that both the insulin function axis and blood pressure regulation could be sensitive targets to oxidative stress programming during the prenatal and early postnatal periods[121-126]. However, there remains a lack of epidemiological data relating biomarkers of perinatal oxidative stress to the metabolic syndrome. Validation of the oxidative stress hypothesis would suggest new early interventions to stem the modern epidemic of the metabolic syndrome.

Prenatal hypoxia programming

There is some evidence linking prenatal hypoxia to increased vulnerability to metabolic and cardiovascular diseases[127]. Chronic hypoxia is a common insult to the fetus and reduced uteroplacental blood flow can result in fetal IUGR independently of malnutrition[128-130]. Chronic prenatal hypoxia has been shown to increase the susceptibility of the adult heart to ischemia-reperfusion injury[131]. Human studies at high altitude also suggest that prenatal hypoxia can result in LBW[132-134]. Chronic hypoxia has profoundly adverse effects on cardiac development and function in the fetus[129] and enhanced β1-adrenergic receptor signaling may induce cardiomyocyte apoptosis *via* a protein kinase A-dependent mechanism[132]. Animal studies show that chronic hypoxia could increase the heart-to-body weight ratio in the fetus, suggesting an asymmetric growth of the heart[133]. Chronic hypoxia significantly increased the levels of cytochrome C, a mitochondrial marker protein, in the fetal heart[134]. The increased cytochrome C levels are likely a metabolic adaptation in the myocardium during asymmetric enlargement of the heart in hypoxic fetuses. Animal experiments showed that mitochondrial biogenesis played an important role in the early stages of cardiac hypertrophy[128]. Hypoxia could induce apoptosis in cultured neonatal rat cardiomyocytes[135]. In response to chronic hypoxia during gestation, many genes related to cell signaling and survival are down- or up-regulated in the fetal heart and other tissues[127]. No epidemiological data are available as to whether these effects are transient or permanent.

Placental dysfunction

It has been proposed that adult cardiovascular and metabolic diseases originate via developmental plasticity and adaptations arising from failure of the maternal-placental nutrient supply to match fetal requirements[136]. This hypothesis emphasizes the role of the placenta in fetal programming. Maternal nutrition was associated with fetal development and programming of human cardiovascular and metabolic disease[137]. Maternal body composition and nutrition intake may affect fetal development by direct effects on substrate availability to the fetus and indirect effects via changes in placental function and structure[136]. Fetal adaptations may result from alterations in placental growth and vascular resistance, altered nutrient and hormone metabolism in the placenta and changes in nutrient transfer and partitioning between mother, placenta and fetus[138-140]. Fetal cardiovascular adaptations, alterations in fetal body composition and changes in fetal endocrinology and metabolism may have long-term effects

on postnatal health. However, no data are available on the epidemiological associations between pathological placental changes and the metabolic syndrome in the offspring. The hypothesis implies that improving placental function may have lifelong health benefits.

Reduced stem cell number

After organogenesis, the ability of cells to divide substantially for self-renewal and repair is limited although some stem cells remain in various tissues in postnatal life. The stem cell hypothesis suggests that IUGR is associated with a reduced number of tissue stem cells, leading to an early exhaustion of organ function when demands are increased greatly[141]. The time windows for stem cell proliferation may represent critical periods. Diabetes patients often have fewer β-cells prior to the onset of disease or the pancreas failed to generate more β-cells in response to an increased demand for insulin[142]. In rats, fetal and neonatal nutritional deprivation caused permanent reductions in β-cell mass and functional efficiency, resulting in glucose intolerance in adulthood[143]. IUGR induced by bilateral uterine artery ligation in pregnant rats caused postnatal glucose intolerance and insulin resistance in offspring; the β-cells mass of IUGR rats was reduced by one-third[144]. There is a lack of data on stem cell number as it relates to metabolic syndrome programming in humans.

OVER-NUTRITION PROGRAMMING?

Although most research is focused on adverse programming associated with poor fetal growth, there is evidence that maternal overnutrition or fetal overgrowth may result in an offspring phenotype susceptible to the metabolic syndrome[145]. Maternal high fat or cholesterol overfeeding during pregnancy and lactation in rodents resulted in a phenotype of the offspring that closely resembled the human metabolic syndrome[145,146]. Gestational diabetes is associated with glucose oversupply to the fetus and consequently fetal macrosomia and may have adverse metabolic programming effects[147]. The effects of gestational diabetes seem independent of genetic factors[148]. Experimental evidence indicates that overnutrition may program obesity and metabolic syndrome through epigenetic changes[114]. A meta-analysis showed a U-shaped relationship between birth weight and type 2 diabetes risk in humans[149]. The hypothesis is concordant with the increasing birth weights over recent decades and may partly explain the increasing prevalence of the metabolic syndrome. It is unclear whether the effects of fetal overgrowth programming could be largely explained by impaired maternal glucose tolerance in humans.

CONCLUSION

The various hypotheses for interpreting developmental programming could be interrelated, indicating the need for research to address multiple mechanisms simultaneously.

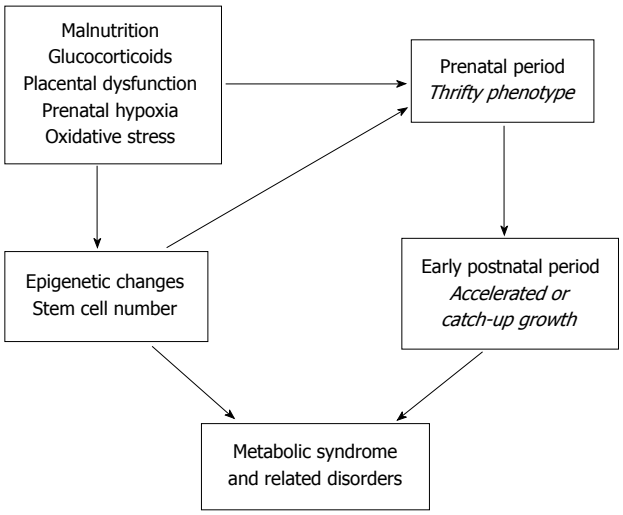

Figure 2 Pieces of the puzzle - potential links between current hypotheses to interpret the mechanisms of developmental programming of the metabolic syndrome and related disorders.

Some mechanisms could be driven by other "driver" mechanisms (Figure 2). Multiple overarching drivers may exist: malnutrition, glucocorticoids, oxidative stress, prenatal hypoxia and placental dysfunction. These drivers may act alone or in combinations to induce epigenetic changes or reduce stem cell number, leading to the thrifty phenotype often followed by catch-up growth and the propensity to metabolic syndrome. Thus, adverse programming may occur in the absence of poor fetal growth.

The current prevailing theory is that fetal programming effects are magnified over the life course. However, the postnatal environment may either mask or magnify the true effects of programming - the direction of effect modifications is unknown. The strongest evidence supporting the various hypothetical mechanisms comes from animal models. However, we cannot assume that findings from animal models are applicable to humans as human pregnancy physiology is much more complex. For example, preeclampsia (gestational hypertension with proteinuria) is a gestational complication unique to humans[150]. Even the commonly used operating definitions for retarded or excessive fetal growth in humans are largely arbitrary and need re-evaluations[151]. There is a need for studies to address multiple mechanisms simultaneously in animal models and a need for prospective pregnancy cohort data linking intrauterine environmental biomarkers of the proposed programming mechanisms to clinical outcomes or surrogate biomarker endpoints in humans. A better understanding of the programming mechanisms is a prerequisite for developing early life interventions to halt the worldwide increasing epidemic of the metabolic syndrome, type 2 diabetes and other related disorders.

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