Received: 30 March 2021 | Revised: 22 May 2021 | Accepted: 24 May 2021

DOI: 10.1111/eci.13625

REVIEW

WILEY

Metabolic Disease Programming: From Mitochondria to Epigenetics, Glucocorticoid Signalling and Beyond

Luís F. Grilo[1,2] | **Carolina Tocantins**[1] | **Mariana S. Diniz**[1] | **Rodrigo Mello Gomes**[3] | **Paulo J. Oliveira**[1] | **Paulo Matafome**[4,5,6,7] | **Susana P. Pereira**[1,8]

[1]CNC - Center for Neuroscience and Cell Biology, CIBB - Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal

[2]PhD Programme in Experimental Biology and Biomedicine (PDBEB), Institute for Interdisciplinary Research (IIIUC), University of Coimbra, Coimbra, Portugal

[3]Department of Physiological Sciences, Biological Sciences Institute, Federal University of Goiás, Goiânia, Brazil

[4]Center for Innovative Biomedicine and Biotechnology (CIBB), University of Coimbra, Coimbra, Portugal

[5]Coimbra Institute for Clinical and Biomedical Research (iCBR) and Institute of Physiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[6]Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal

[7]Department of Complementary Sciences, Instituto Politécnico de Coimbra, Coimbra Health School (ESTeSC), Coimbra, Portugal

[8]Laboratory of Metabolism and Exercise (LametEx), Research Centre in Physical Activity, Health and Leisure (CIAFEL), Laboratory for Integrative and Translational Research in Population Health (ITR), Faculty of Sport, University of Porto, Porto, Portugal

Correspondence
Susana P. Pereira, CNC-Center for Neuroscience and Cell Biology, UC Biotech, Biocant Park, University of Coimbra, 3060-197 Cantanhede, Portugal.
Email: pereirasusan@gmail.com

Funding information
Foundation for Science and Technology, Grant/Award Number: DFA/BD/5539/2020, POCI-01-0145-FEDER-016657, PTDC/DTP-DES/1082/2014, SFRH/BPD/116061/2016, Summer Course (15-20/7/245), UIDB/04539/2020 and UIDP/04539/2020; NIH, Grant/Award Number: R01HD070096-01A1

Abstract

Embryonic and foetal development are critical periods of development in which several environmental cues determine health and disease in adulthood. Maternal conditions and an unfavourable intrauterine environment impact foetal development and may programme the offspring for increased predisposition to metabolic diseases and other chronic pathologic conditions throughout adult life. Previously, non-communicable chronic diseases were only associated with genetics and lifestyle. Now the origins of non-communicable chronic diseases are associated with early-life adaptations that produce long-term dysfunction. Early-life environment sets the long-term health and disease risk and can span through multiple generations. Recent research in developmental programming aims at identifying the molecular mechanisms responsible for developmental programming outcomes that impact cellular physiology and trigger adulthood disease. The identification of new therapeutic targets can improve offspring's health management and prevent or overcome adverse consequences of foetal programming. This review summarizes recent biomedical discoveries in the Developmental Origins of Health and Disease (DOHaD) hypothesis and highlight possible developmental programming mechanisms, including prenatal structural defects, metabolic (mitochondrial dysfunction, oxidative stress, protein modification), epigenetic and glucocorticoid signalling-related mechanisms suggesting molecular clues for the causes and consequences of programming of increased susceptibility of offspring to metabolic disease after birth. Identifying mechanisms involved in DOHaD can contribute to early interventions in pregnancy or

early childhood, to re-set the metabolic homeostasis and break the chain of subsequent events that could lead to the development of disease.

KEYWORDS

ageing-related disease, Developmental Origins of Health and Disease (DOHaD), developmental programming, malnutrition, metabolism, non-communicable diseases

1 | INTRODUCTION

Foetal programming results from prenatal adaptations during embryonic and foetal development to achieve a new developmental balance, leading to a new physiological homeostatic state. This foetal ability to adapt to different intrauterine environments increases the immediate survival and improves success in an adverse environment increasing the chances of survival to the organism. However, inapt interpretations or postnatal environmental deviations can prime a mismatch between prenatal predictions and postnatal experience, making disadvantageous that adaptation.

Several stimuli in the early stages of life are a consequence of an impairment of the intrauterine environment by placental and/or maternal conditions, such as obesity, undernutrition, lack of vitamins or micronutrients, alcohol consumption, smoking, a compromised vascular system, placental dysfunction, hormonal milieu (eg maternal stress), physical activity and xenobiotic exposure among others.[1-3]

Epidemiologic and experimental evidence suggests that foetal programming can permanently affect organ structure and physiological function predisposing to long-term disease, with an emphasis on chronic non-communicable diseases, such as cardiovascular diseases (CVD) and diabetes (Table 1).[4-7] The association between intrauterine environment and postnatal disease was first described by Barker, whose hypothesis postulates that the foetus is programmed by stimuli or insults during early life, determining adulthood health and disease.[8]

The foetal stage is a critical period of rapid cell differentiation in which organs and tissues are quickly developing. Alterations in nutrient supply in early and late gestation can affect foetal growth and tissue growth and maturation, compromising organ postnatal function independently of genetic influence. These organ-specific modifications act to increase short-term foetal survival at the cost of long-term adverse consequences.[1] The mechanisms involved are not well-defined, but a relationship between altered structural development of the organs and persistent cellular changes is assumed, even if a latency period exist and disease only manifest in adult life.

Foetal programming alterations often lead to a homeostatic state that presents lower metabolic plasticity and lower adaptability to postnatal insults, predisposing to early development of chronic disease (eg metabolic, cardiovascular and endocrine disease).[9-11] Specific stimuli, mostly of maternal origin, may affect foetal gene expression, which may lead to foetal programming at any stage of development. Some alterations induce temporary adaptations, while others can persist throughout adult life or even generations.

The decreased foetal metabolic plasticity may persist throughout offspring life, affecting both the metabolic-endocrine regulation and cellular metabolism, including modifying mitochondrial function. Mitochondria play a critical role in postnatal metabolic maturation, especially in the prenatal to postnatal transition associated with the rise of oxygen circulating levels and increased energetic dependence on mitochondrial bioenergetics. Thus, it is likely that mitochondrial metabolic regulation and dysfunction play a role in foetal programming, either by direct modulation of the metabolism or through induction of cellular damage. Recent data suggest a crosstalk between mitochondria and epigenetics in several diseases, including cancer, proposing a potential relationship between metabolic remodelling and long-term regulation of gene expression. Whether this relation is observed throughout foetal development and/or plays a role in metabolic disease programming is still an open question.

The foetal metabolic remodelling may be also originate by the compromised biological function of biomolecules through modifications, such as glycation and oxidation. The induced alterations may persist until adulthood or at least act in foetal programming by promoting premature metabolic dysfunction. Organ hypertrophy or hyperplasia as also being described, as well as modification of the organ structure, vascularization, innervation and juxtaposition that can perpetually alter metabolism.[12-15] Several molecular mechanisms have also being proposed, including acute or chronic changes in gene expression, through various avenues and abnormal cell growth due to specific metabolic conditions.[14]

This review aims to discuss foetal adaptations to a suboptimal intrauterine environment, to debate the mechanisms that lead to a new prenatal physiological homeostatic state, and how these alterations modulate offspring's future health and disease. In this review, we specifically focused on foetal adaptations in terms of (a) metabolic programming affecting mitochondrial function and oxidative stress; (b) metabolite-related irreversible protein modification; (c) long-term epigenetic remodelling of gene expression; and (d) endocrine

TABLE 1 Major findings in foetal programming studies

Model	Approach	Tissue	Sample size	Major findings	Reference
Four-week-old female C57Bl/6 mice	High-fat high-sugar diet	Skeletal muscle	n = 4	Offspring exposed to maternal obesity showed decreased OXPHOS activity (especially complexes II, III and V)	122
Female C57BL/6J mice	High energy diet	Foetal tissue (various)	-	Foetal tissues derived from maternal obesity resulted in repressive histone methylation in the Zfp423 promotor	172
Mice	Mx1-Cre-expression Hdac3-null	Liver	-	Liver-specific Hdac3 knock out led to hepatocyte hypertrophy, a shift in carbohydrate and lipid metabolism, and increased hepatic and circulating triglycerides and cholesterol	160
Male and female C57BL/6J mice	11β-HSD2$^{+/+,\pm,-/-}$	Placenta	n = 6-15	Low vascularization and reduced nutrient and amino acid transport in the placenta resulted in IUGR offspring	193
C57Bl/6J mice	Sodium butyrate administration through diet supplementation	Skeletal muscle	n = 5-10	Class I and II HDAC inhibition led to improvement in obesity-induced metabolic dysfunction, oxidative fibres number, and mitochondrial function by PGC-1α gene promoter exposure	163
C57Bl/6J mice	Knockdown of the class IIa HDACs	Liver	n = 4-9	Hepatocyte's depletion of class IIa HDACs led to FOXO hyperacetylation	158
Apolipoprotein E null mice	Second-hand smoke, carbon monoxide and nicotine in utero exposure	Heart (aortas)	n = 8	84 days old offspring of mothers exposed to second-hand smoke showed high levels of ROS	126
Female and male C57BL/6 mice	AGEs rich diet	Various	n = 4	Offspring of mothers subjected to high-AGE or high-fructose diets during pregnancy showed increased predisposition for weight gain, adiposity, liver fat, and insulin resistance	83
Male and female albino Wistar rats	Sweet sugar beverages diet with sucrose or HFCS-55	Various	n = 19-25		84
Sprague-Dawley rats	50% of daily food intake (11 g/day)	Skeletal muscle	-	Increased HDAC1/4-related histone deacetylation and MEFA2A repression interactions in adult IUGR might result in GLUT4 expression perturbation	165
Female Wistar rats	Daily subcutaneous nicotine bitartrate injection	Pancreas	n = 15	Rat offspring exposed to nicotine during foetal development showed augmented ROS levels	116
Wistar rats	Isoenergetic diets containing casein and folic acid	Liver	-	Protein restriction during pregnancy resulted in the hypomethylation of individual CpG dinucleotides in the glucocorticoid receptor and peroxisome proliferator-activated receptor α, resulting in increased mRNA expression	203
Female Wistar rats	Dexamethasone subcutaneous administration	Liver	n = 8-33	Permanent overexpression of phosphoenolpyruvate carboxylase was induced by increased glucocorticoid receptor expression, potentiating glucose intolerance and insulin resistance in adulthood	197
Female Wistar Rats	Calcium-deficient diet	Liver	n = 5	A calcium-deficient diet resulted in hypomethylation in specific CpG dinucleotides of the Hsd11b1 and Nr3c1 genes promoter region	204

(Continues)

TABLE 1 (Continued)

Model	Approach	Tissue	Sample size	Major findings	Reference
Sprague-Dawley rats	Diabetes induction with streptozotocin administration via tail vein	Foetal tissue (various)	n = 16-19	Maternal diabetes resulted in high levels of (carboxymethyl)lysine in the embryos and low levels of vascular endothelial growth factor	73
Wistar rats	Diabetes induction with streptozotocin injection	Heart	n = 5-30	Newborns of streptozotocin-induced diabetic rats showed high levels of AGEs and oxidative stress and inflammatory markers	74
Wistar rats	Isocaloric low protein (LP) (8%) diet	Skeletal muscle	n = 6-8	Increased levels of 4-hydroxynonenal, protein tyrosination, and OXPHOS complexes II, II-III, and IV were observed in offspring born to mothers on a caloric restriction diet	123
Sprague-Dawley rats	Intraperitoneal xylazine and ketamine anaesthesia and uterine arteries ligation	Liver and pancreas (β-cells)	n = 7	Increased levels of ROS in IUGR offspring of dams due to hydroxynonenal regulated protein modification	115
Welsh Mountain sheep	Foetal cortisol infusion or maternal dexamethasone treatment	Blood	n = 5-6	Mammalian target of rapamycin and ribosomal protein S6 kinase phosphorylated forms were decreased due to cortisol infusion while dexamethasone treatment led to increased GLUT4 expression	202
Romney ewes	Undernutrition	Blood	n = 6-8	Maternal undernutrition resulted in hypomethylation of the glucocorticoid receptor and proopiomelanocortin gene promoter in offspring	205
Sheep	Dexamethasone intravenous administration	Heart (cardiac mitochondria)	n = 8-9	Steroid exposure during pregnancy led to higher levels of mitochondrial superoxide production in the offspring	114
Non-human primates (baboons)	High-fat energy diet	Blood	n = 5-22	Foetal baboons showed disrupted methionine and folate cycles through a decrease in the levels of circulating intermediates	138
Non-human primates (adult Japanese macaques)	Western-style diet	Skeletal muscle	n = 3-28	High levels of lipid peroxidation products, thiobarbituric acid reactive substance and hydroxynonenol–modified proteins in offspring of obese non-human primates	118
Human	Overweight and obese women (criteria: maternal age (18-35 years), singleton gestation <34 weeks at time of enrolment, normal foetal anatomy, carrying a male foetus)	Skin fibroblasts	n = 14	Offspring of obese women showed increased levels of superoxide and protein carbonylation, concomitant with increased ROS and oxidative stress levels	127
Human	Women with gestational diabetes mellitus	Umbilical cord mesenchymal stromal cells	n = 3-4	Gestational diabetes mellitus led to increased levels of superoxide anion in the offspring's umbilical cord mesenchymal stromal cells	128
Human	Individuals prenatally exposed to famine during the Dutch Hunger Winter	- (Epigenetics, DNA)	n = 60-62	Prenatal exposure to maternal undernourishment resulted in lower DNA methylation patterns of the imprinted IGF2 gene at 60 years old, compared with same-sex siblings whose mothers has a regular nutrition	178

(Continues)

TABLE 1 (Continued)

Model	Approach	Tissue	Sample size	Major findings	Reference
Human	Individuals born before <32 weeks of gestation and/or with very low birth weight (<1.500 g) in 1983	- (Epigenetics, DNA)	n = 38-75	Small for gestational age individuals showed different DNA methylation patterns in IGF2, GNASAS, INSIF and LEP gene loci, compared to infants born with appropriate weight for gestational age	180
Female Sprague Dawley rats	Total enteral excess calories nutrition	Foetal tissue (various)	n = 7	High birth weight was related to increased DNA methylation of the glucocorticoid receptor, while prenatal exposure to gestational diabetes mellitus indicated lower DNA methylation in MEST and NR3C1	173
Human	Mothers with dietetically treated, and with insulin-dependent gestational diabetes mellitus	Placenta	n = 57-88		182
Human	Mothers with gestational diabetes mellitus	Placenta	n = 460		181
Human	Young adults (23-28 years) born preterm whose mothers received antenatal steroids	Heart and blood	n = 16-32	Young adults showed decreased levels of β-cell homeostasis, resultant from reduced insulin and increased glucose levels	199
Human	Unbalanced diet during pregnancy	Blood	n = 34	Specific methylation patterns in the promoter region of the HSD2, H19 and IGF2 gene were related to increased blood pressure and obesity	206
Human	Healthy nonsmoking pregnant women	Placenta (trophoblasts)	n = 3-6	AGEs accumulation and AGE receptor activation was associated with oxidative stress, inflammation processes, low levels of hCG and apoptosis in the first trimester	71
Human	Prepubertal children born full-term and singleton from mothers without carbohydrate metabolism alterations during pregnancy	Blood	n = 130	Overweight children with high and low birth weight had decreased levels of AGE receptor soluble isoforms sRAGE and esRAGE, which were associated with insulin resistance	72

impairment of stress responses through cellular receptors and/or messengers' breakdown, as potential mechanisms linked to foetal programming to draw the complex network that dictates the organism health and disease.

1.1 | Maternal influence on foetal growth and birthweight

Epidemiological evidence indicates a clear relationship between term birthweight and offspring predisposition to early or later life disease.[4,5,6,7,16] Birthweight is widely used as a marker of healthy foetal growth. This relationship is a result of the adverse foetal milieu challenge to the foetus. Understanding the physiological mechanisms that imprint the challenge to foetal programming outcome and its association with future disease is critical for developing new therapeutic approaches and breaking the disease intergenerational transmission link (eg obesity, diabetes, CVD). Interestingly, foetal growth potential is determined by placental development, which, in turn, depends on maternal physiology rather than genetics.[17] Birthweight correlates better among siblings with the same maternal origin rather than paternal, and it is strongly associated with recipient weight rather than donor weight in oocyte donation cases.[17,18]

The placenta plays a critical role in maternal-foetal interaction by regulating the foetal nutritional supply and composition. A normal placental function is critical to regulate developmental programming.[19-22] Maternal physiology and nutrition control placental development and function by epigenetic modulation of transporter expression and activity.[20,23] Lack or excess of maternal circulating nutrients and the resultant effects on foetal nutrient delivery via the placenta are the most studied challenges underlying foetal programming.[23,24]

Glucose is the primary metabolic/energetic substrate for the placenta and foetus, crucial for prenatal growth since foetal gluconeogenesis is minimal.[21] Glucose concentration in the foetal circulation depends on maternal glucose circulating levels and placental partial buffering.[21,22,25] Maternal hyperglycaemia due to diabetes and/or obesity stimulates foetal insulin secretion, favouring anabolic reactions (eg lipogenesis and protein synthesis) and increasing foetal glucose consumption in insulin-sensitive cells (hepatocytes, myocytes, adipocytes), leading to increased growth, rising glucose requirements in late gestation and eventually inducing insulin resistance.[26] Maternal hyperglycaemia has been associated with offspring obesity later in life.[27] In contrast, maternal undernutrition, characterized by low maternal glucose circulating levels, leads to intrauterine growth restriction (IUGR).[28,29] In these cases, due to low substrate availability, the foetal metabolic rate is reduced to improve foetal viability.[1] IUGR resulting from many causes, including maternal smoking, foetal anaemia, foetal hypoxia or placental dysfunction, has been associated with increased incidence of offspring's metabolic and CVD later in life.[2,27,29,30]

Alterations in the maternal endocrine system can affect foetal gene expression during development and interfere with prenatal growth. Placental endocrine and metabolic activity also impact foetal development through increased placental mitochondrial oxidative/nitrative stress or inflammatory-response pathways stimulation.[31,32] Foetal and placental insulin-like growth factor (IGF) 2 stimulates foetal growth, whereas reduced IGF2 receptor expression acts as a growth inhibitor.[33-36] Additionally, IGF1 levels in umbilical cord blood positively correlate with birthweight.[37] Nutritional deficiency during gestation can lead to foetal growth hormone resistance, impair foetal growth and associate with future development of diabetes, osteoporosis and CVD.[38] It has been demonstrated that maternal glucocorticoid secretion rises at late gestation.[39] Even though cortisol is partially inactivated by 11β-hydroxysteroid dehydrogenase (11β-HSD) during placental translocation to the foetal circulation, prenatal exposure to increased maternal glucocorticoids associates with low birthweight, resetting the offspring's hypothalamic-pituitary-adrenal (HPA) axis and the predisposition for metabolic disorders in adulthood.[40,41]

1.2 | Maternal glucose metabolism and influence on foetal organs growth

Altered nutrient availability can lead to non-genetic-related organ structural dysfunction that compromises future function.[2] Poor maternal nutrition and low foetal glucose availability can result in hypoplasia of the endocrine pancreas and decreased pancreatic β-cell mass.[5,42,43] This structural defect results in insulin hyposecretion throughout foetal development and foetal growth restriction, potentially leading to increased susceptibility to diabetes prevalence in adult offspring. An impairment of pancreatic β-cell development directly affects foetal, and postnatal endocrine pancreas function with secondary effects on the metabolic programming of insulin sensitivity and cellular downstream signalling pathways in insulin-dependent organs (eg heart, liver, adipose tissue).[26,44]

In contrast, maternal diabetes associates with larger foetal pancreatic islets, foetal hyperinsulinemia and macrosomia.[45] Interestingly, the increase in foetal weight is mainly a consequence of the increased weight of insulin-dependent organs.[44] Functional hyperinsulinemia during brain development affects the regulation of metabolism and homeostatic energy regulatory systems due to the programming of the hypothalamic metabolic regulation centres.[1,7] These findings are consistent with the observation of an increased incidence of obesity and diabetes among the offspring of diabetic mothers.[46] However, the detailed molecular mechanisms behind this relationship remain undetermined.

In the setting of maternal undernutrition and IUGR conditions, foetal brain development is prioritized through foetal blood redistribution to increase foetal viability.[29,47] In this situation, many other organs, especially post ductal such as the kidney and liver, are vulnerable to growth restriction. Both kidney size and nephron number decrease in the presence of IUGR, compromising adult kidney function, glomerular filtration rate, water accumulation predisposing to hypertension after body weight increase.[48-50] Liver function is also impaired by growth restriction. Birth abdomen circumference, usually related to liver size, inversely correlates with adult serum concentration of low-density lipoprotein (LDL) cholesterol and fibrinogen, suggesting that a compromised liver function in adulthood is a consequence of IUGR.[51,52]

Foetal heart development is highly dependent on nutritional supply.[53] The prenatal to postnatal transition results in a switch from hyperplasic to hypertrophic cardiomyocyte growth and loss of proliferative ability.[54,55] The *in utero* programming of cardiomyocyte number and maturation is critical for future heart function.[56] Maternal malnutrition results in fewer cardiomyocyte number and inadequate maturation already observed in early stages.[57] Cardiomyocyte immature metabolism (mainly fuelled by the glycolytic pathway) leads to foetal cardiac hypertrophy (different from the adult hypertrophy-related increase in contractile elements) and may persist throughout life.[11] Maternal diabetes stimulates foetal cardiomyocyte proliferation while inhibiting its maturation through the pentose phosphate pathway.[58] This leads to heart hypertrophy due to a high number of cardiomyocytes with lower contractile capability and the enrichment of apoptotic cells induced by increased mitochondrial production of reactive oxygen species (ROS).[59] Foetuses of obese sheep show increased blood glucose and insulin, altered phosphorylation

of AMP-activated protein kinase (AMPK) and other key signalling pathways. Although the hearts' contractility of foetuses from obese mothers was normal in the basal state, impaired heart rate, left ventricular developed pressure was observed in response to high workload stress. These findings indicate poor cardiac reserve and adaptability increasing the predisposition to later life insulin resistance and cardiac dysfunction.[60] In vitro function of isolated cardiomyocytes in foetuses of obese sheep showed impaired cardiomyocyte contractility through altered intracellular Ca^{2+} handling, overloading of foetal cardiomyocyte intracellular $Ca^{2+,}$ and aberrant myofilament protein composition.[61]

In summary, the intrauterine environment can directly influence the health status by changing the structural development of the organs, altering cell number and maturation. However, foetal programming may result from cellular alterations that can predispose to disease later in life. Foetal nutrient availability throughout gestation can affect the organism's metabolic maturation and compromise foetal-neonatal transition at a cellular level. Beyond malnutrition by undernutrition or obesity, it is important to bear in mind that offspring's disease programming can also occurs due to the nutrition quality. Unfortunately, this topic has been poorly studied.

2 | MECHANISM OF METABOLIC DISEASE PROGRAMMING

2.1 | Early exposure to glycotoxins and metabolic impairment in adult life

Maternal diet can expose the offspring to glycotoxins both in foetal and neonatal stages. Glycotoxins are mainly formed endogenously as a result of hyperglycaemia or exogenously during cooking, especially fast dry-heat cooking, which increases the rate of glycotoxins formation. Glycotoxins include irreversible products, such as advanced glycation end-products (AGEs), and their precursors, such as methylglyoxal (MG), a by-product of glucose and fructose metabolism. MG modifies arginine and lysine residues of proteins and DNA, forming AGEs.[62-65] As reviewed by Matafome et al, 2017, AGEs may be formed physiologically through modification of intracellular (cytoplasmic proteins and transcription factors), circulating (haemoglobin, albumin or lipoproteins) and extracellular matrix proteins, modifying the activity of the proteasome and protein quality control pathways and increasing oxidative and nitrosative stress in different cell types.[62] The formation of extracellular AGEs may activate membrane receptors, such as RAGE, which triggers intracellular inflammatory and oxidative pathways.[66] Such mechanisms are implicated in the degenerescence of insulin-independent cells (endothelial cells, podocytes and neurons) and diabetic complications (retinopathy, nephropathy and peripheral neuropathy).[62] Moreover, glycotoxins have been implicated in the pathophysiology of cardio- and cerebrovascular and degenerative diseases and the long-term loss of β-cell viability and insulin resistance development. Although lean models' findings were controversial, insulin resistance was consistently observed in obese animal models with increased glycosative stress, while AGE-restricted diets improve insulin sensitivity in normal, overweighed and diabetic patients.[62] Although glycotoxins are associated with diabetes complications and the deterioration of metabolic status, the impact of early glycotoxin exposure since the perinatal period is almost entirely unknown. Recent evidence has suggested that such exposure may increase the risk of metabolic dysregulation and related complications in adult life, becoming pertinent to discuss the impact of the different sources of newborn exposure to glycotoxins and later life metabolic implications.

Women with GDM have increased serum and placental levels of MG and AGEs such as carboxymethyllysine (CML), being correlated with oxidative stress, inflammation, insulin resistance and vascular disease.[67-70] In human trophoblasts, AGEs accumulation and RAGE activation were associated with oxidative stress, inflammation, low hCG levels and apoptosis in the first trimester, leading to implantation impairment of placentation and embryonic development.[71] Accordingly, decreased levels of the soluble RAGE isoforms (sRAGE and esRAGE) found in overweight prepubertal children who had high (HBW) or low birthweight (LBW) were correlated with insulin resistance.[72]

In animal models, higher CML levels in the embryos of diabetic female rats were also associated with lower VEGF levels.[73] Similarly, newborns of STZ-induced diabetic rats had higher content of AGE oxidative stress and inflammatory markers in the heart and increased hippocampal RAGE expression, neuronal excitability and behavioural changes.[74,75] Comparably, gestational glyoxalase pathway disruption was associated with premature neurogenesis, depletion of cortical neural precursor cells and behavioural changes.[76] On the other hand, RAGE knockout prevented embryonic dysmorphogenesis in the offspring of diabetic rats.[77]

AGEs are absorbed by the placenta, and AGE levels in the blood of lactating mothers and in their infants were correlated.[78,79] Accordingly, high consumption of refined carbohydrates and sugar-sweetened soft beverages consumption during pregnancy correlate with offspring congenital heart defects, newborn small for gestational age and increased risk of offspring overweight.[80-82] In animal models, increased predisposition for weight gain, adiposity, liver fat and insulin resistance was observed in the progeny of females fed a high-AGE or high-fructose diet during pregnancy.[83,84]

Recent studies demonstrated that breastfeeding is related to overweight and glucose intolerance in children from diabetic mothers.[85] These observations may suggest that AGE

effects may also occur through lactation. Increased skin AGEs levels were found in infants of mothers with smoking habits during lactation, showing that AGEs may transmit through breastmilk.[86] In animal models, increased glycotoxin levels were observed in cows' milk maintained with a high AGEs diet.[87] In a study by Francisco *et al*, the oral administration of MG to breastfeeding rats conducted to increased milk glycotoxins content and impaired lipid profile and β-cell function, and more adiposity in the offspring.[88]

Infant formulas are typically rich in sugars and proteins, and their industrial production includes heat exposition, increasing their AGEs, such as (carboxymethyl)lysine (CML), for almost 35-fold higher than in the breastmilk of healthy mothers.[89,90] Their absorption was confirmed in previous studies demonstrating a correlation between formula AGEs and their circulating levels and excretion in newborns.[89,91] Although not a consensual issue, the intestinal absorption of AGEs like pyrraline and CML was proven in adults, and dietary AGE restriction was shown to reduce their plasma concentration and renal excretion.[92-94] Dietary AGEs were also shown to change gut microbiota diversity in rats and humans, reducing short-chain fatty acid-producing bacteria and damaging colonic epithelial barrier.[95,96] Although AGE absorption in the neonatal gut has never been addressed, the immaturity and permeability of the newborn's gut may also allow glycotoxins absorption.[97] Newborns' orally delivered MG was lethal in concentrations 4 times lower than in adult male rats, suggesting an increased susceptibility to dietary glycotoxins in newborns (531mg/kg vs. 1990 mg/kg).[98]

Mericq and colleagues (2010) showed a rapid increase of serum CML and methylglyoxal derivatives in the infant's blood after introducing infant formulas.[79] Conversely, exclusive breastmilk feeding was shown to prevent the insulin resistance associated with an AGEs-rich formula; however, the mother's diet, including the cooking method, is also a critical factor.[79,99] In animal models, consumption of an AGEs-rich formula during suckling increased CML accumulation in renal tubular cells and increased levels of oxidative stress and inflammation markers in adult life.[100,101]

Increased perinatal exposure to glycotoxins may predispose to the development of oxidative stress, inflammation and insulin resistance, which may increase the risk of diabetes and other associated pathologies in adult life. Even in type 1 diabetes, exposure to increased dietary AGE levels during pregnancy and lactation deteriorates β-cell function in the progeny, while maternal dietary AGE restriction reduced T-cell inflammatory activity in the pancreas.[102] Uncontrolled diabetes may increase foetal exposure to high AGEs levels, and proper glycaemic control should decrease such risk. Recently, cut-off values for mothers' glycated albumin levels during pregnancy were suggested to prevent neonatal complications.[103] The available evidence suggests that breastmilk from mothers with diabetes or consuming a Westernized diet is rich in MG and AGEs and may have a significant impact on the health and development of the neonate, potentially contributing to the development of cardiometabolic disorders in adulthood, although more studies are necessary to clarify the mechanisms involved. Available evidence also directly implicates infant formulas' nutritional composition, increasing the newborn's glycosative stress and disease propensity.

2.2 | Mitochondrial and oxidative stress mechanisms as programmers of offspring metabolism

Adequate mitochondrial function is essential to support both the mother and the foetus' energetic demands during pregnancy.[104] Foetal mitochondrial biology's modulation can play an unfavourable role in foetal programming, contributing to the memory for offspring metabolic disease manifestation.[29,50,105] Mitochondria function is greatly stimulated in most cells in prenatal to postnatal transition due to the rise in oxygen circulating levels.

Oxygen levels appears to impact this transition. Pregnant mice exposed to hypoxia show decreased placental respiration rates and reduced mitochondrial oxidative capacity, indicating that placental mitochondria are altered by the prevailing environment *in utero*.[19] Impaired mitochondrial function was also described in the human placenta from obese women.[106]

Postnatal mitochondrial dysfunction was reported for the offspring of obese mothers, especially in organs with high energetic requirements, such as the heart,[107] skeletal muscle,[108,109] liver,[110] hypothamalus,[111] pancreas,[112] and adipose tissue.[113] Indeed, mitochondrial dysfunction is common in foetal and postnatal tissues due to different maternal stressors,[50,114,115,116,117,118] resulting in an increased predisposition for CVD,[119] non-alcoholic fatty liver disease (NAFLD),[120] obesity and type 2 diabetes,[121] making clear that mitochondrial function can be modulated in the foetal stage, with those alterations likely to persist in postnatal life.[29]

The impact of maternal nutritional intervention during pregnancy on foetal and offspring mitochondrial function presents mixed results. For example, in a mice model of diet induced-maternal obesity by high-fat high-sugar (HFHS) the offspring exhibited decreased OXPHOS activity in skeletal muscle, namely for complexes II, III and V.[122] In a rat model of maternal caloric restriction, Tarry-Adkins et al showed an increase in OXPHOS activity, namely complexes II, II-III and IV, in the offspring skeletal muscle and increased levels of 4-Hydroxynonenal (HNE).[123] This data exemplify how mitochondrial response differs according to animal model, maternal stress factor and offspring tissue analyzed,[124] raising the hypothesis that maternal stress effects on offspring metabolism and development is stimuli and tissue-dependent.

The programming of mitochondria during foetal development affects its postnatal proper function. Mitochondrial dysfunction is related to metabolic modulation, and it may lead to cellular oxidative stress since mitochondria are a source of reactive species production, especially during metabolic stress.[114] ROS are important signalling molecules and together with protein-function modulation by oxidative damage, constitute a potential mechanism for mitochondrial memory (Figure 1).[125] ROS and reactive nitrogen species (RNS) participate in cell defence mechanisms, metabolism, growth, and differentiation. During pregnancy, ROS and RNS play a vital role in foetal gene transcription and organogenesis, acting as signalling molecules required for a successful gestation.[124] However, unbalanced increased ROS levels can damage mitochondrial DNA (mtDNA), nuclear DNA and other cellular components. Thus, a disruption in this redox balance may act as a foetal programming mechanism, as supported by different animal models. Peterside et al demonstrated that HNE-modified proteins were increased in pancreatic β-cells and in the livers of rat offspring exposed to gestational IUGR,[115] while non-human primates born to obese mothers fed with a high-fat diet (HFD) presented increased thiobarbituric acid reactive substance (TBARS) and 4-HNE in skeletal muscle, reflecting increased oxidative stress.[118]

Exposure to second-hand smoke or nicotine is also related to programming of offspring metabolic disease, resulting from oxidative stress. For example, nicotine exposure during foetal development induced higher pancreatic ROS levels later in rat offspring life, indicated by increased fluorescence of 2',7'-dichlorodihydrofluorescein diacetate (H_2DCFDA).[116]

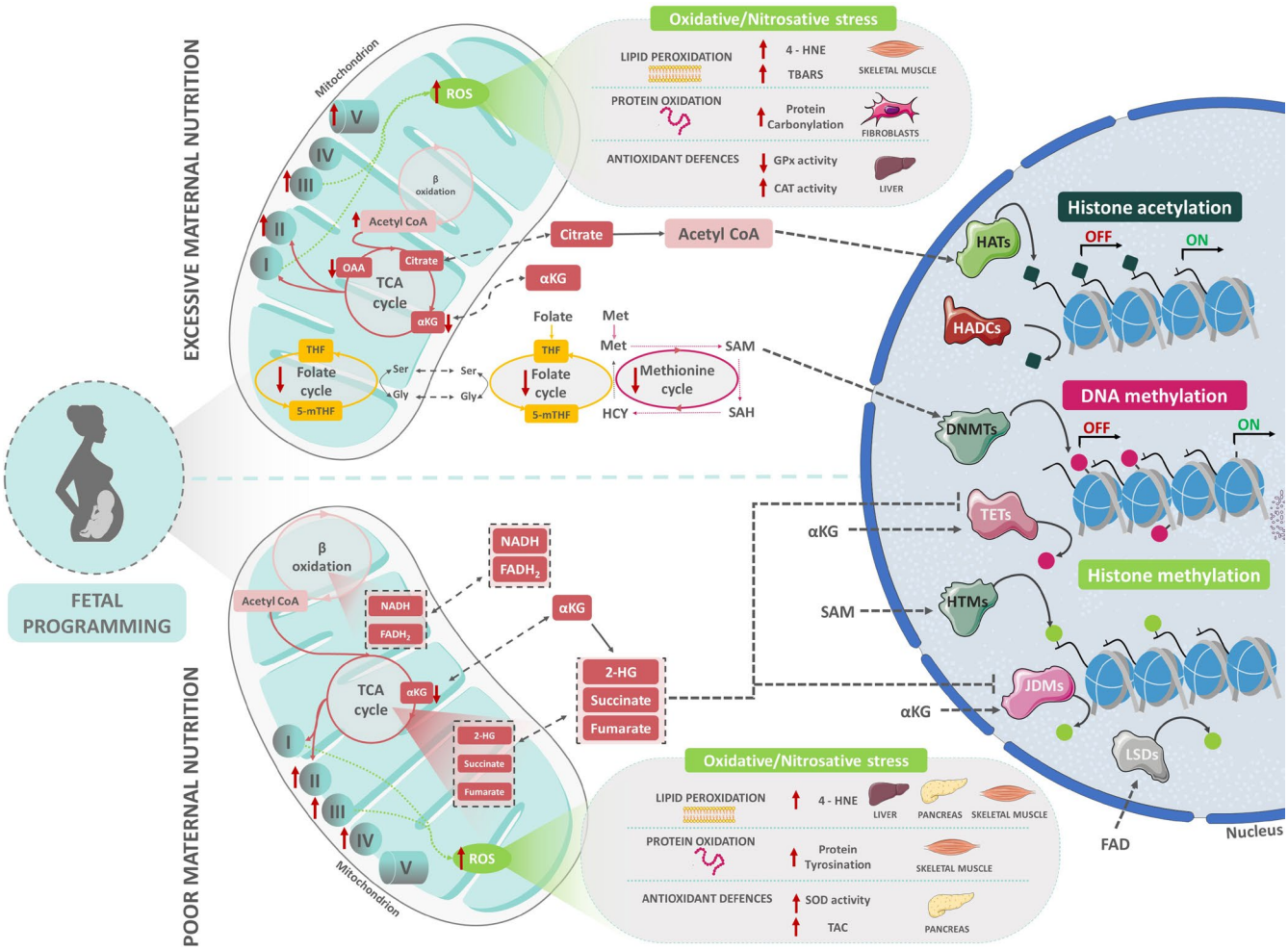

FIGURE 1 The mitochondrial maternal imprinting for disease in the offspring. The hepatic mechanisms for the mitochondria-epigenetics crosstalk in foetal programming influence metabolites on epigenetic regulation across two different maternal stress factors: maternal nutrient excess leading to maternal obesity (MO) and maternal nutrient restriction leading to intra-uterine growth restriction (IUGR). Alterations in mitochondrial metabolism during foetal development impact neonatal and adult metabolism through direct programming of metabolic pathways, epigenetic modulation of metabolic gene expression, and oxidative and nitrosative damage. The regulation of mitochondrial pools of different metabolites impacts on cytosolic and nuclear pools, which regulate the enzymes responsible for the epigenetic profile. Mitochondrial redox state also impacts on oxidative/nitrosative stress influencing lipid peroxidation, protein oxidation and antioxidant defence mechanisms in different tissues for MO and IUGR

In the same line, maternal exposure to second-hand smoke led to increased ROS production in the aortas of mice 84 days after birth, indirectly measured by aconitase enzymatic activity.[126] In a sheep model, offspring exposed to steroids during pregnancy showed higher levels of mitochondrial superoxide production in the hearts.[114]

Human studies corroborate these general findings in animal models. For example, exposure to maternal obesity increased ROS and oxidative stress, leading to increased superoxide anion and protein carbonylation in offspring fibroblasts a few days after birth.[127] In another work, an increase in superoxide anion production was verified in umbilical cord mesenchymal stem cells extracted at birth, from mothers with gestational diabetes mellitus (GDM).[128]

To counterpart higher concentrations of these oxidative molecules, antioxidant defences, such as catalase, glutathione system and superoxide dismutase, are produced in an attempt to maintain the redox balance.[125] Oxidative stress occurs when an imbalance between the overproduction of reactive species or less active antioxidant capacity, or even a combination of both occurrences is verified in a specific cellular compartment.[129] Thus, maternal stress factors could induce oxidative stress (Figure 1), highlighting the possibility that oxidative stress has a causative relation to mitochondrial programming *in utero*. Consistently, animal models showed higher ROS production and levels of oxidative stress biomarkers along with an altered antioxidant capacity in offspring born to different sorts of maternal stress factors, for example nutrition or smoking. The offspring of mice with MO showed impaired antioxidant capacity, namely increased hepatic catalase levels and decreased glutathione peroxidase 1 (GPx1) levels.[130] In piglets, increased activities of SOD and total antioxidant capacity were also detected in the offspring subjected to IUGR throughout foetal development.[131] MO during pregnancy induced testicular and sperm oxidative stress in male offspring, as suggested by the elevated MDA levels and reduced SOD and GPx activities, which decreased the viability motility and induced more abnormalities in sperm, compromising fertility.[132] Interventions that impact mitochondria and oxidative stress, such as antioxidants consumption and gestational practice of physical exercise, could potentially revert deleterious foetal programming effects.[133-136]

Mitochondrial dysregulation in early life due to maternal stress conditions could have severe consequences for the offspring later in life. Further studies are needed to clarify the mechanisms by which mitochondria are imprinted for future disease, depending on the tissue and maternal-induced intrauterine insult. The present knowledge suggests three possible mechanisms of foetal programming involving mitochondria in the complex metabolic network: direct programming of mitochondrial function *in utero*, foetal dysregulation of ROS signalling pathways and oxidative damage due to unbalanced oxidative/antioxidant mechanisms. More profound knowledge about these mechanisms could be relevant for implementing an intervention, treatment or even prevention strategies to avert disease in infants born to mothers with stress factors.

Epigenetic modifications are other potential mechanisms that lead to mitochondrial metabolic memory imprinting for future disease.[137] Physiological alterations have been described in several metabolic-related pathways due to foetal programming, including methionine and folate cycles,[138] hepatic accumulation of triglycerides,[130,139] and intracellular levels of acetyl-CoA, α-ketoglutarate, among other metabolites,[140] all with implications in epigenetic regulation. Therefore, exploring the mitochondria-epigenetics crosstalk (Figure 1) could be noteworthy since it could unravel the mechanisms by which mitochondria could induce and acquire memory for disease.

2.3 | Epigenetics programming resulting from metabolic alterations

Epigenetics refers to mechanisms that can regulate gene expression without any alterations in the DNA sequence. These mechanisms consist in modifications of chromatin, histones and DNA, playing a central role in DNA packing. These dynamic chromatin structure modifications activate or repress specific genes' transcriptional state through mechanisms involving histone post-translational modifications or DNA methylation.[141] More recently, non-coding microRNAs were described as key components of epigenetic control.[142]

The modulation of epigenetics profile is crucial during foetal development to determine the biological fate and establish tissue-specific gene expression patterns.[143] Therefore, embryonic and foetal development is a period with high epigenetic plasticity, after which the epigenome is relatively stable over time, and only a fraction presents modulation by ageing and environmental stimuli, such as diet and physical activity.[144-146] Moreover, epigenetic marks are mitotically stable, emphasizing the importance of intrauterine milieu-modulated epigenome in long-term gene expression and, consequently, disease programming at adulthoood.[147]

Oocyte DNA is hypomethylated before implantation and in the morula stage, and starts to suffer methylation during embryogenesis, regulating organogenesis and differentiation.[143] Methylation reduces gene expression and regulates epigenetic memory through single nucleotide alteration, most commonly 5-methylcytosine (5mC), typically in CpG islands.[148] DNA methylation is regulated by ten-eleven translocation (TET) enzymatic activity, which triggers the demethylation process, and DNA methyltransferases (DNMTs: DNMT1, DNMT3A and DNMT3B) activity.[147,149] While DNMT1 is responsible for the mitotic maintenance of DNA methylation pattern, DNMT3A and DNMT3B regulate de novo DNA

methylation.[150] DNMTs require SAM as a methyl donor, meaning that intermediate metabolism, including methionine and folate cycles, is critical to DNA methylation.[151] In opposition, TETs enzymatic activity requires α-ketoglutarate, Fe(II) and oxygen, while it is inhibited by succinate, fumarate and 2-hydroxyglutarate.[149,152] Maternal high-fat high-energy diet disrupted methionine and folate cycles in foetal baboons through the decrease of circulating intermediates.[138]

Histone acetylation is related to transcriptional activation, being regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) activities and acetyl-CoA availability from intermediate metabolism. While high cellular levels of acetyl-CoA promote histone acetylation, low concentrations represent a slower cellular metabolism and are associated with suppressing gene expression through decreased histone acetylation.[153-155] Moreover, HDACs activity requires NAD^+ as a cofactor and depends on available intracellular pools and cellular metabolic rate.[156]

Histone modification associates with metabolism regulation and metabolic disease including obesity and diabetes.[157] Class IIa HDACs phosphorylation by LKB1-dependent kinases leads to cytoplasmatic sequestration, preventing histone deacetylation. Class II HDACs' dephosphorylation, as a response to glucagon, allows the translocation to the nucleus and proper function.[158] These mechanisms regulate hepatic gluconeogenesis due to class IIa HDACs association with G6pc and Pck1 promoters.[159] Hepatocytes class IIa HDACs depletion induces FOXO hyperacetylation, while the Hdac3 liver-specific knockout resulted in hepatocyte hypertrophy, shifted carbohydrate and lipid metabolism, and increased hepatic and circulating triglycerides and cholesterol.[158,160]

HDACs play an essential role in regulating skeletal muscle metabolic gene expression.[161] Class IIa HDAC represses MEF2-dependent transcription by direct interaction in nucleus and repression of metabolism-related genes including PGC-1α, hexokinase-II, ATP synthase β and CPT-1.[162] Class I and II HDAC inhibition by sodium butyrate intake by obese mice improved metabolic dysfunction, skeletal muscle oxidative fibres number and mitochondrial function by PGC-1α gene promoter exposure.[163] Significantly, HDAC3 liver recruitment has been associated with Rev-erbα-regulated circadian gene expression regulation, thus regulating hepatic lipid homeostasis.[164] Skeletal muscle HDAC1- and HDAC4-related histone deacetylation and MEF2A repression were proposed as mechanisms of GLUT4 expression perturbation in IUGR adult female rat offspring predisposing to diabetes.[165]

Moreover, during an obesogenic pregnancy in mice, an increased accumulation of triglycerides in the offspring's livers was demonstrated, requiring increased levels of cytosolic acetyl-CoA to promote de novo lipogenesis.[130] This factor could influence the activity of histone acetyltransferases.[166] Thus, the histone acetylation could be mediated, in part, by the cytosolic levels of acetyl-CoA, as demonstrated in MO Japanese macaque offspring, which showed higher levels of triglycerides along with increased acetylation of histone H3 in multiple residues, corroborating the previous observations.[139]

Histone methylation requires SAM and represents the balance between activities of histone methyltransferases (HTMs) and histone demethylases (HDMs). Metabolite pools also regulate HDMs activity: lysine-specific demethylases (LSD) require FAD as a cofactor and Jumonji C domain demethylases (JMJD) α-ketoglutarate.[167] HMTs depend on SAM generations by cytosolic methionine-homo-cysteine cycle and mitochondrial folate cycle, and ATP.[168] HMTs, namely SET domain lysine methyltransferases 7 (SETD7), inhibit mitochondrial biogenesis through PGC-1α and antioxidant response activation NFE2L2.[169]

Increased histone methylation (H3K4me3) and acetylation (Histone 3) during terminal adipocyte differentiation have been linked with PPARγ and C/EBPα gene expression, contributing to early adipogenesis and predisposing for obesity.[170,171] Repressive histone methylation (H3K27me3) in Zfp423 promoter, a key transcription factor for adipogenic lineage commitment, was decreased in foetal rodent tissues due to maternal obesity leading to increased Zfp423 gene expression, promoting adipogenic differentiation, programming adiposity and metabolic dysfunction later in life.[172,173] Besides that, α-ketoglutarate, a TCA cycle intermediate, could interfere with histone methylation through JMJD activity regulation. Decreased hepatic α-ketoglutarate have been shown in a non-human primate (NHP) model of MO offspring.[140] This could explain the altered histone post-translational modifications caused by maternal diet.[139]

Epigenetics and metabolism crosstalk play an essential role in health and disease.[174] Firstly, epigenetic modulation of gene expression can programme cellular metabolism, the balance between anabolic and catabolic pathways, and mitochondrial OXPHOS through stoichiometric regulation of complexes subunits expression.[175-177] Secondly, mitochondria can control gene expression by the retrograde response of the mitonuclear communication and regulate the epigenome through regulation of critical epigenetic metabolites availability such as acetyl-CoA and S-adenosyl methionine (SAM).[175] Since mitochondria are sensitive to foetal programming, the cellular energy status and mitochondrial function are likely to play a critical role in epigenome modulation.

During the Dutch Hunger Winter, individuals exposed to maternal malnutrition still presented, after six decades, lower DNA methylation of the imprinted IGF2 gene than same-sex siblings with regular maternal nutrition.[178] Other genes also related to growth, development, and energy metabolism presented DNA methylation alterations.[179] DNA

methylation patterns were different in IGF2, GNASAS, INSIGF and LEP gene *loci* compared to infants born with small or appropriate weight for the gestational age.[180] In contrast, the glucocorticoid receptor gene's DNA methylation in the human placenta was increased with high birthweight, while decreased MEST and glucocorticoid receptor NR3C1 genes were found in cord blood and placenta from prenatal exposure to GDM.[181,182]

Epigenetic modulation is now accepted as a part of metabolic disease development and preservation. Whether these epigenetic mechanisms could be imprinted throughout foetal development due to the maternal environment and persist until adult life, contributing to disease predisposition is not entirely understood. Epigenome studies throughout the life of offspring from a stressful intrauterine milieu can help to understand epigenetic persistence assess whether the memory mechanisms are reversible and identify the most critical periods in metabolic disease programming.

2.4 | Glucocorticoid signalling during pregnancy and metabolic stress: a link to epigenetics

Glucocorticoids (GCs), also known as 'stress hormones', have long been recognized to play critical functions in maintaining organism homeostasis by regulating energy metabolism, inflammation state and other biological processes.[183] Synthetized by the adrenal glands, their secretion is tightly controlled by the HPA axis (Figure 2). In response to environmental insults (eg malnutrition, stress, infection), the hypothalamus releases a corticotrophin-releasing hormone (CRH), stimulating the neurons in the anterior pituitary to secrete the adrenocorticotropic hormone (ACTH), which delivers the signal for GC secretion.[184] GCs bind to the GC receptor (GR) in target tissues, resulting in its translocation to the nucleus to regulate the transcription of specific genes, such as Pck, Igfbp1, G6pc, among others.[183,185]

Altered regulation of the HPA axis may be the cause or the consequence of epigenetic regulation of gene expression,

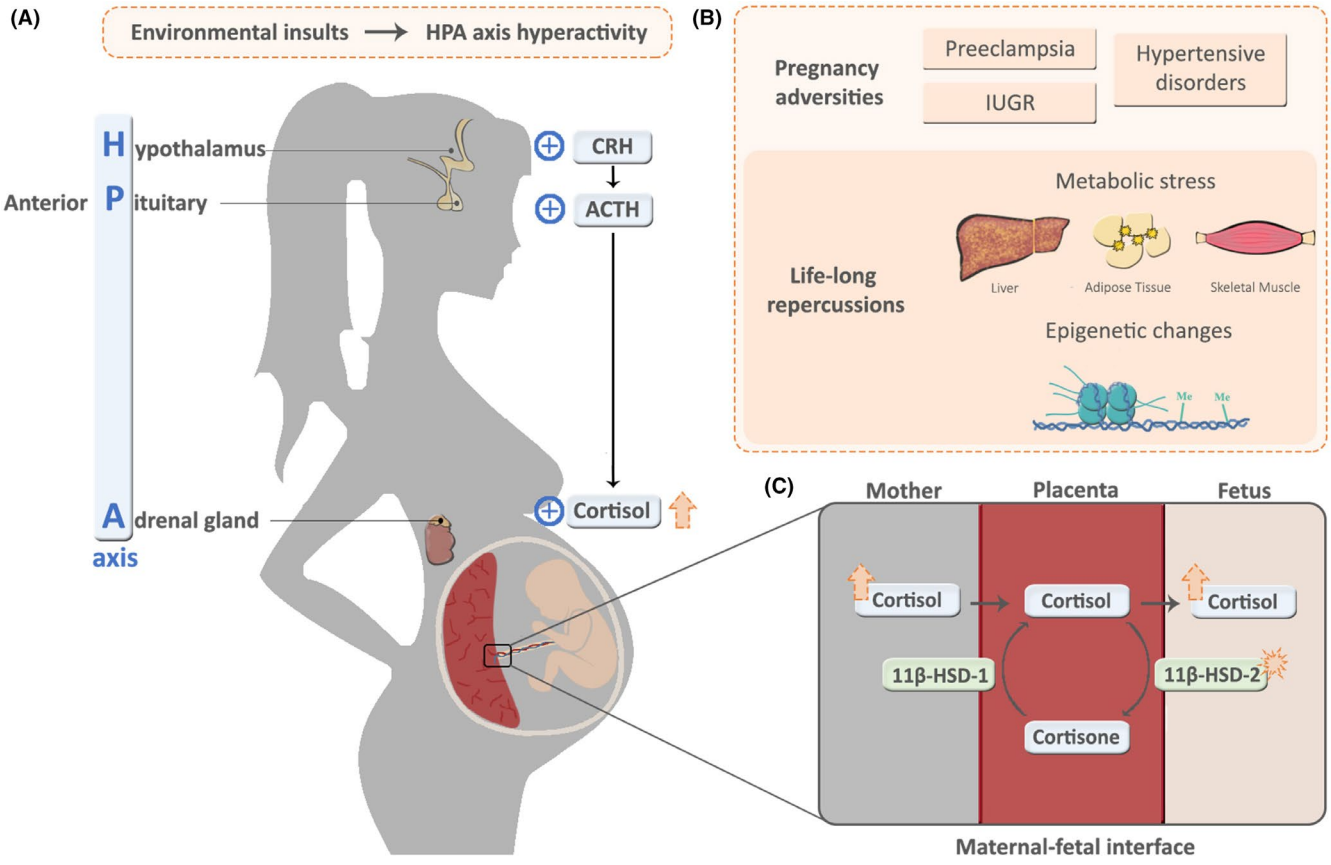

FIGURE 2 Glucocorticoid signalling during pregnancy, regulation and long-life implications. The physiological secretion of glucocorticoids is controlled by the hypothalamic-pituitary-adrenal (HPA) axis, which is stimulated mainly during pregnancy (A). The placenta plays a vital role in regulating cortisol levels that reach the foetus, expressing a vital enzyme, 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), that converts cortisol to its inactive form, cortisone (C). When subjected to stressful insults, the mother's HPA axis may undergo overstimulation, resulting in intrauterine cortisol overexposure, dysregulation of 11β-HSD2 and consequent hyperactivity of the foetus HPA axis. These alterations could lead to pregnancy adversities, such as preeclampsia, intrauterine growth restriction (IUGR), hypertensive disorders and life-long repercussions caused by early metabolic stress and potential epigenetic changes (B)

which could control metabolic and mitochondrial function. Time-dependent studies throughout foetal development are critical to clear the temporal modulation of the pathways, which enter then in a vicious cycle of adaptations and culminate in the programming of a new foetal physiological balance that may last the lifetime.

The maternal HPA axis undergoes remarkable adjustments and stimulation during the challenging period of pregnancy.[40] In early pregnancy, GCs are essential for implantation, decidualization and preventing embryo rejection by cross-reaction with the maternal immune system.[183] Throughout gestation, the maternal adrenal glands gradually become hypertrophic due to the placental secretion of CRH.[186] Consequently, during the second and third trimesters, a peak in cortisol concentration occurs, leading to a 3- to 8-fold increase in total serum levels.[187] Concomitantly, the foetal adrenal glands transiently produce cortisol from ~7 to 10 weeks of gestation, increasing the production gradually in the third trimester.[41] Maternal malnutrition can affect cortisol metabolism and modulate foetal exposure.[188-192] GCs have an essential role in foetal preparation to extra-uterine life, contributing to foetal organ systems' maturation, particularly the respiratory and digestive systems. In this regard, synthetic GCs are commonly used in pregnancies with a significant risk for preterm delivery to accelerate lung maturation and improve the viability of the newborn.[186,188]

Since maternal GCs can cross the placenta and reach the foetus, GC trafficking must be tightly regulated. The expression of 11β-HSD isoforms is responsible for GC transport from the maternal to foetal circulation (Figure 2). 11β-HSD-1 isoform acts as a reductase and is responsible for converting biologically inactive cortisone into its active form, cortisol. 11β-HSD-1 is expressed in various maternal-foetal interface tissues, except in the syncytiotrophoblast, in which the expression of 11β-HSD-2 prevails. This enzyme is responsible for the conversion of cortisol into inactive cortisone.[40,186] Therefore, 11β-HSD-2 acts as a physiological shield to prevent excessive foetal exposure to maternal cortisol.[40,183,186]

In utero GC overexposure has been associated with pregnancy adversities, such as preeclampsia, hypertensive disorders, and IUGR (Figure 2). Hsd11b2 null mice exhibited low placental vascularization and reduced placental nutrient and amino acid transport, resulting in an IUGR environment.[193] Correlations between reduced placental 11β-HSD-2 expression/activity and IUGR in human pregnancies have also been established.[194,195] This suggests that GC placental handling might represent a mechanism through which the intrauterine environment influences foetal development and, when dysregulated, results in foetal GC overexposure, which might constitute an early stressor contributing to life-long programming of diseases through increased activity of the offspring's HPA axis.[196]

This may result in the GR's differential expression in the various tissues crucial for organ development and several systems' homeostatic function, including the metabolic system. Liver GR expression was higher in the offspring of rats treated with dexamethasone, the most commonly used synthetic GC, when administered in late gestation, inducing permanent overexpression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) and potentiating glucose intolerance and insulin resistance in adulthood.[197] Changes in the adipose tissue due to dexamethasone exposure can potentiate insulin resistance development.[198] Furthermore, exposure to synthetic GCs during pregnancy led to decreased levels of homeostasis model assessment for β-cell function (HOMA-β) in young adults due to lower insulin and higher glucose levels.[199]

Unfortunately, the majority, if not all, of the studies are based on the evaluation of metabolic stress programming by late gestation exposure to dexamethasone.[193,197,198,199] It is essential to consider that, in the current days, metabolic syndrome is a great pandemic that affects people mostly from developing and developed countries.[200,201] Malnutrition is also problematic due to the emerging socio-economic discrepancies observed in the last decades.[201] Therefore, the repercussions and perpetuation of lifestyle habits that might increase GC levels, such as malnutrition and lack of physical activity, deserve further attention from others, especially during pregnancy. Jellyman et al studied the effects of dexamethasone and cortisol in the ovine foetus's skeletal muscle and observed differences in the two treatments' metabolic responses. Cortisol infusion led to decreased levels of mammalian target of rapamycin (mTOR) and ribosomal protein S6 kinase (S6K) phosphorylated forms, while dexamethasone led to increased glucose transporter-4 (GLUT4) expression,[202] consistent with the observed hyperglycaemia induced by maternal dexamethasone administration among other studies.[197,198]

Whether prenatal stress might compose a factor inducing permanent changes in genes involved in the regulation and modulation of the HPA axis and associated metabolic responses through DNA methylation has been the recent research focus (see section **Epigenetics programming**) in animal models and humans. In the former, offspring of rats subjected to a protein restriction diet during pregnancy presented hypomethylation of individual CpG dinucleotides in the GR and peroxisome proliferator-activated receptor alpha (PPAR-α) promoter, which regulates lipid metabolism, leading to increased mRNA expression in the liver.[203] Liver tissue of neonatal offspring of dams subjected to a calcium-deficient diet showed hypomethylation in specific CpG dinucleotides of the Hsd11b1 and the GR gene (Nr3c1) promoter.[204] Finally, maternal undernutrition in a sheep model was associated with GR gene promoter hypomethylation in the foetal hypothalamus and the proopiomelanocortin (POMC) gene,

both intimately involved in hypothalamic energy balance by regulation of food intake mechanisms.[205] The data were confirmed in humans. A study involving adult offspring of mothers with an unbalanced diet during gestation established associations between methylation patterns in the promoter region of specific genes (HSD2, H19, IGF2) and increased blood pressure and obesity.[206]

The role of GCs during pregnancy and foetal development is critical to guarantee foetal survival. The 'window' and length of GC exposure throughout gestation are specific, and impairments in their regulatory system can lead to pregnancy complications and the development of life-long diseases.[194,195] Furthermore, treatment with synthetic GCs and endogenous GC overexposure may result in different metabolic responses. Although advances are taking place in understanding the specific triggers of foetal GC overexposure and driven repercussions, how GCs directly affect foetal development and programme the offspring of mothers subjected to stressful insults during gestation are still unclear. Coupled with the observations of epidemiological studies, the advances in epigenetics and the use of animal models have a tremendous value to study this matter and unravel the mechanisms through which GC might contribute to foetal programming of metabolic stress and consequent chronic diseases in adulthood.

3 | CONCLUSIONS

Metabolic, cardiovascular and endocrine disease incidence have been increasing worldwide over the last decades. Even though it is partially a consequence of some postnatal lifestyle factors, including diet and lack of physical exercise, epidemiological observations pointed out perinatal maternal stressors and diet throughout gestation and lactation as factors that change the intrauterine environment, compromising foetal development and predisposing for future disease (Figure 3).

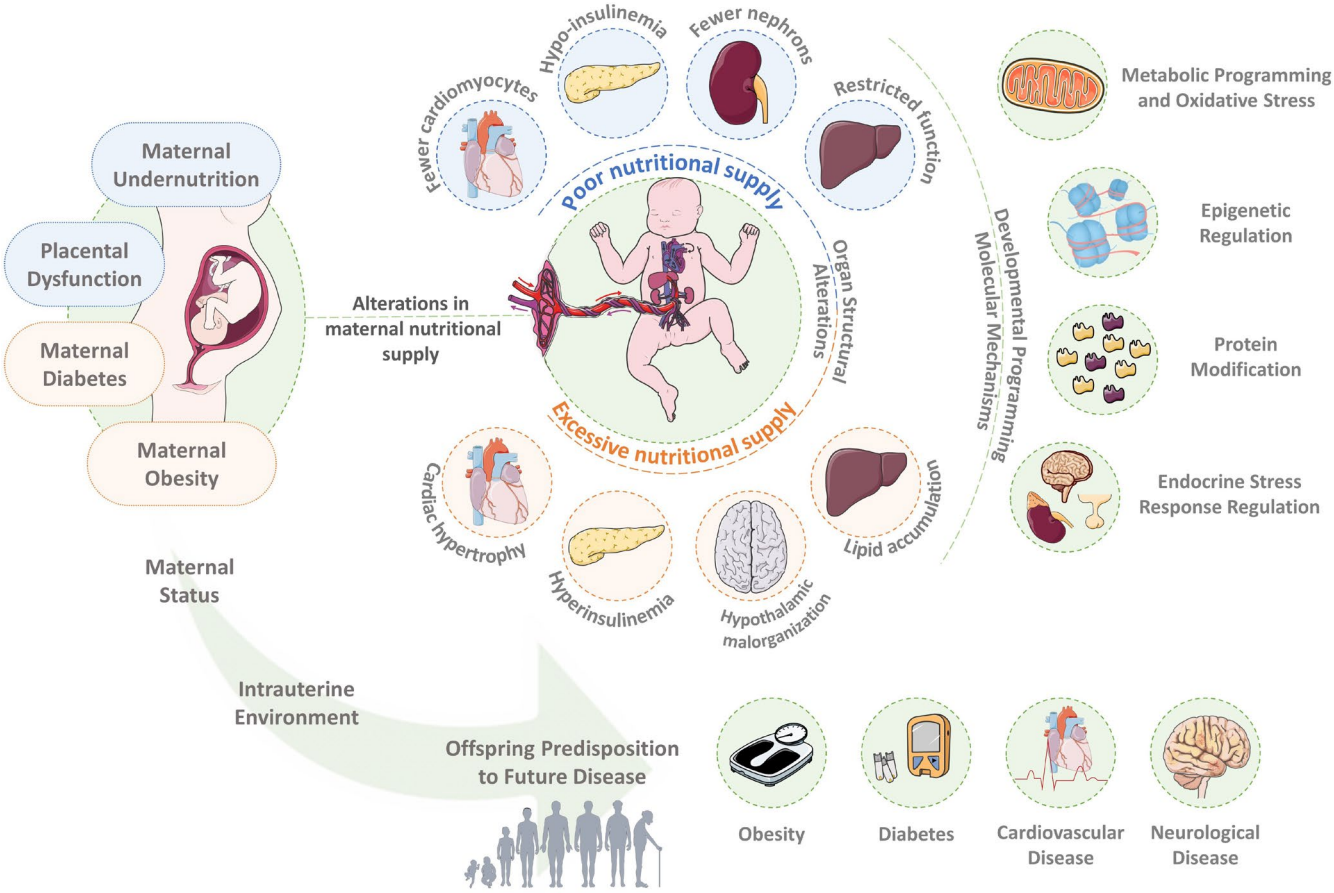

FIGURE 3 Maternal foetal programming proposed mechanisms that predispose the offspring to long-term disease. The intrauterine environment is mainly regulated by maternal status, such as nutrition and placental functionality. Alterations in maternal metabolism, immunity, inflammation and endocrine system change the foetus's intrauterine environment by modulating the foetal nutrient supply. These maternal alterations can imprint foetal tissues predisposing the offspring for disease, including obesity, diabetes, cardiovascular and neurological disease, leading to an intergenerational cycle of metabolic disease transmission by two layers: the first one comprises the direct compromise of the foetal tissues due to congenital defects, such as cardiac hypertrophy, hyper/hypoinsulinaemia and hepatic lipid accumulation; the second layer includes foetal programming consequences, which can occur through cellular and molecular mechanisms, including metabolic programming, oxidative stress, protein modification and endocrine dysregulation. All these alterations can trigger events in the future that predispose the offspring to disease

Although significant knowledge has been accumulating in the field, longitudinal studies regarding the memory-based mechanisms that contribute to disease predisposition are still missing and the identification of particular foetal programming metabolic pathways is needed. We here described some of the most likely potential mechanisms, namely mitochondrial dysfunction, oxidative stress, endocrine impairment, glycation and oxidation of biomolecules and epigenetic remodelling. A combination of two or more of those mechanisms may influence foetal metabolic programming in the cell and tissue level, being the outcome tissue and stimuli-dependent.

A deeper understanding of the memory-based mechanisms stimulated *in utero* can contribute to break this intergenerational disease transmission. Identifying the cellular pathways and critical timepoints of their activation is essential to develop new therapeutic and strategic approaches to prevent foetal programming of disease in specific temporal windows. For effectively battle metabolic diseases, which are a great burden of worldwide health, it is imperative to contemplate the concerns involving early gestation, metabolic programming and epigenetics. The implementation of health strategies throughout critical phases of development, comprising pregnancy, lactation and puberty, is crucial to accomplish long-term consistent outcomes and prevent the perpetuation of metabolic diseases.

ACKNOWLEDGMENTS

We acknowledge Peter W. Nathanielsz for his contribution in discussing this manuscript. The research was funded by ERDF through the Operational Programme Competitiveness Factors—COMPETE2020, and national funds by Foundation for Science and Technology under FCT-Post-doctoral Fellowship (SPP, SFRH/BPD/116061/2016), FCT-doctoral Fellowship (LFG, DFA/BD/5539/2020), LFG, CT and MSD were supported by the project 'Summer Course in Interdisciplinary Research, Development and Innovation in Cellular and Molecular Metabolism' (15-20/7/245), funded by the FCT and Directorate General for Higher Education (DGES), project grant PTDC/DTP-DES/1082/2014(POCI-01-0145-FEDER-016657), strategic project UIDB/04539/2020, UIDP/04539/2020 and NIH grant R01HD070096-01A1. The funding agencies had no role in study design, data collection and analysis, decision to publish or preparation of this document.

ORCID

Luís F. Grilo http://orcid.org/0000-0002-6278-9241
Carolina Tocantins http://orcid.org/0000-0002-3758-0454
Mariana S. Diniz http://orcid.org/0000-0002-2161-9676
Rodrigo Mello Gomes http://orcid.org/0000-0002-9012-3287
Paulo J. Oliveira https://orcid.org/0000-0002-5201-9948
Paulo Matafome https://orcid.org/0000-0002-3422-290X
Susana P. Pereira https://orcid.org/0000-0002-1168-2444

REFERENCES

1. Kwon EJ, Kim YJ. What is fetal programming?: a lifetime health is under the control of in utero health. *Obstet Gynecol Sci*. 2017;60:506-519.
2. Miranda JO, Ramalho C, Henriques-Coelho T, Areias JC. Fetal programming as a predictor of adult health or disease: the need to reevaluate fetal heart function. *Heart Fail Rev*. 2017;22:861-877.
3. Ruchat SM, Hivert MF, Bouchard L. Epigenetic programming of obesity and diabetes by in utero exposure to gestational diabetes mellitus. *Nutr Rev*. 2013;71:S88-S94.
4. Hales CN, Barker DJ, Clark PM,, et al. Fetal and infant growth and impaired glucose tolerance at age 64. *Br Med J*. 1991;303:1019-1022.
5. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992;35:595-601.
6. Hales CN, Barker DJP. The thrifty phenotype hypothesis. *Br Med Bull*. 2001;60:5-20.
7. Hales CN, Ozanne SE. The dangerous road of catch-up growth. *J Physiol*. 2003;547:5-10.
8. Barker DJP. In utero programming of chronic disease. *Clin Sci*. 1998;95:115-128.
9. Hogg K, Wood C, McNeilly AS, Duncan WC. The in utero programming effect of increased maternal androgens and a direct fetal intervention on liver and metabolic function in adult sheep. *PLoS One*. 2011;6:1-12.
10. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol*. 2017;5:53-64.
11. Ahmed A, Delgado-Olguin P. Embryonic programming of heart disease in response to obesity during pregnancy. *Biochim Biophys Acta - Mol Basis Dis*. 2020;1866:165402.
12. Kuo AH, Li C, Li J, Huber HF, Nathanielz PW, Clarke GD. Cardiac remodelling in a baboon model of intrauterine growth restriction mimics accelerated ageing. *J Physiol*. 2017;595:1093-1110.
13. Kuo AH, Li C, Li J, Huber HF, Nathanielz PW, Clarke GD. Poor perinatal growth impairs baboon aortic windkessel function. *J Dev Orig Health Dis*. 2017;5038:1-6.
14. Guiomar de Almeida Brasiel P, Cristina Potente Dutra Luquetti S. Metabolic Programming and Nutrition. In New Insights Into Metabolic Syndrome vol. 32 137-144 (IntechOpen, 2021).
15. Fall CHD, Kumaran K. Metabolic programming in early life in humans. *Philos Trans R Soc B Biol Sci*. 2019;374:20180123.
16. Nathanielsz P. Life before birth: The challenges of fetal development. undefined (1996).
17. Galliano D, Garrido N, Serra-Serra V, Pellicer A. Difference in birth weight of consecutive sibling singletons is not found in oocyte donation when comparing fresh versus frozen embryo replacements. *Fertil Steril*. 2015;104:1411-1418.e3.
18. Cunningham S, Cameron IT. Consequences of fetal growth restriction during childhood and adult life. *Current Obstet Gynaecol*. 2003;13:212-217.
19. Sferruzzi-Perri AN, Higgins JS, Vaughan OR, Murray AJ, Fowden AL. Placental mitochondria adapt developmentally and in response to hypoxia to support fetal growth. *Proc Natl Acad Sci USA*. 2019;116:1621-1626.
20. Myatt L. Placental adaptive responses and fetal programming. *J Physiol*. 2006;572:25-30.

21. Brett KE, Ferraro ZM, Yockell-Lelievre J, Gruslin A, Adamo KB. Maternal-Fetal nutrient transport in pregnancy pathologies: the role of the placenta. *Int J Mol Sci*. 2014;15:16153-16185.
22. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental growth and metabolism. *Biochim Biophys Acta - Mol Basis Dis*. 2020;1866:165359.
23. Jansson T, Ekstrand Y, Björn C, Wennergren M, Powell TL. Alterations in the activity of placental amino acid transporters in pregnancies complicated by diabetes. *Diabetes*. 2002;51:2214-2219.
24. Hay WW. Placental-fetal glucose exchange and fetal glucose metabolism. *Trans Am Clin Climatol Assoc*. 2006;117:321.
25. Desoye G, Nolan CJ. The fetal glucose steal: an underappreciated phenomenon in diabetic pregnancy. *Diabetologia*. 2016;59:1089-1094.
26. Brown LD, Wesolowski SR, Kailey J, et al. Chronic hyperinsulinemia increases myoblast proliferation in fetal sheep skeletal muscle. *Endocrinology*. 2016;157:2447-2460.
27. Basu M, Garg V. Maternal hyperglycemia and fetal cardiac development: clinical impact and underlying mechanisms. *Birth Defects Res*. 2018;110:1504-1516.
28. Lesage J, Hahn D, Léonhardt M, Blondeau B, Bréant B, Dupouy JP. Maternal undernutrition during late gestation-induced intrauterine growth restriction in the rat is associated with impaired placental GLUT3 expression, but does not correlate with endogenous corticosterone levels. *J Endocrinol*. 2002;174:37-43.
29. Pereira S, Tavares L, Duarte A, et al. Sex dependent vulnerability of fetal nonhuman primate cardiac mitochondria to moderate maternal nutrient reduction. *Clin Sci*. 2021;;135:1103-1126.
30. Fajersztajn L, Veras MM. Hypoxia: from placental development to fetal programming. *Birth Defect Res*. 2017;109:1377-1385.
31. Genbacev O, Zhou Y, Ludlow JW, Fisher SJ. Regulation of human placental development by oxygen tension. *Science (80)*. 1997;277:1669-1672.
32. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care*. 1996;19:257-267.
33. Reik W, Constância M, Fowden A, et al. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *J Physiol*. 2003;547:35-44.
34. Angiolini E, Coan PM, Sandovici L, et al. Developmental adaptations to increased fetal nutrient demand in mouse genetic models of Igf2-mediated overgrowth. *FASEB J*. 2011;25:1737-1745.
35. Dilworth MR, Kusinski LC, Cowley E,, et al. Placental-specific Igf2 knockout mice exhibit hypocalcemia and adaptive changes in placental calcium transport. *Proc Natl Acad Sci USA*. 2010;107:3894-3899.
36. Kadakia R, Josefson J. The relationship of insulin-like growth factor 2 to fetal growth and adiposity. *Horm Res Paediatr*. 2016;85:75-82.
37. Fowden AL, Coan PM, Angiolini E, Burton GJ, Constancia M. Imprinted genes and the epigenetic regulation of placental phenotype. *Prog Biophys Mol Biol*. 2011;106:281-288.
38. Byrne CD. Programming other hormones that affect insulin. *Br Med Bull*. 2001;60:153-171.
39. Jung C, Ho JT, Tropy DJ, et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. *J Clin Endocrinol Metab*. 2011;96:1533-1540.
40. Pofi R, Tomlinson JW. Glucocorticoids in pregnancy. *Obstet Med*. 2020;13:62-69.
41. Johns EC, Denison FC, Reynolds RM. The impact of maternal obesity in pregnancy on placental glucocorticoid and macronutrient transport and metabolism. *Biochim Biophys Acta - Mol Basis Dis*. 2020;1866:165374.
42. Petrik J, Reusens B, Arany E, et al. A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II. *Endocrinology*. 1999;140:4861-4873.
43. Dumortier O, Blondeau B, Duvillié B, et al. Different mechanisms operating during different critical time-windows reduce rat fetal beta cell mass due to a maternal low-protein or low-energy diet. *Diabetologia*. 2007;50:2495-2503.
44. Susa JB, Neave C, Sehgal P, et al. Chronic hyperinsulinemia in the fetal rhesus monkey. Effects of physiologic hyperinsulinemia on fetal growth and composition. *Diabetes*. 1984;33:656-660.
45. Blotsky AL, Rahme E, Dahhou M, Nakhla M, Dasgupta K. Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. *CMAJ*. 2019;191:E410-E417.
46. Perng W, Oken E. Maternal obesity and associated offspring diabetes mellitus. *Nature Rev Endocrinol*. 2019;15:630-632.
47. Rudolph AM. The fetal circulation and its response to stress. *J Dev Physiol*. 1984;6:11-19.
48. Mackenzie HS, Lawler EV, Brenner BM. Congenital oligonephropathy: The fetal flaw in essential hypertension? In Kidney International, Supplement. Kidney Int Suppl. 1996;vol. 55.
49. Manalich R, Reyes L, Herrera M, Melendi C, & Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int*. 2000;58:770-773.
50. Pereira SP, Oliveira PJ, Tavares LC, et al. Effects of moderate global maternal nutrient reduction on fetal baboon renal mitochondrial gene expression at 0.9 gestation. *Am J Physiol - Ren Physiol*. 2015;308:F1217-F1228.
51. Barker DJP, Martyn CN, Osmond C, Hales CN, Fall CHD. Growth in utero and serum cholesterol concentrations in adult life. *Br Med J*. 1993;307:1524-1527.
52. Barker DJP, Meade TW, Fall CH,, et al. Relation of fetal and infant growth to plasma fibrinogen and factor VII concentrations in adult life. *Br Med J*. 1992;304:148-152.
53. Thornburg KL. The programming of cardiovascular disease. *J Dev Orig Health Dis*. 2015;6:366-376.
54. Clubb FJ, Bishop SP. Formation of binucleated myocardial cells in the neonatal rat. An index for growth hypertrophy. *Lab Investig*. 1984;50:571-577.
55. Li F, Wang X, Capasso JM, Gerdes AM. Rapid transition of cardiac myocytes from hyperplasia to hypertrophy during postnatal development. *J Mol Cell Cardiol*. 1996;28:1737-1746.
56. Ellen Kreipke R, Wang Y, Miklas JW, Mathieu J, Ruohola-Baker H. Metabolic remodeling in early development and cardiomyocyte maturation. *Semin Cell Dev Biol*. 2016;52:84-92.
57. Barbera A, Giraud GD, Reller MD, et al. Right ventricular systolic pressure load alters myocyte maturation in fetal sheep. *Am J Physiol - Regul Integr Comp Physiol*. 2000;279:1157-1164.
58. Nakano H, Minami I, Braas D, et al. Glucose inhibits cardiac muscle maturation through nucleotide biosynthesis. *Elife*. 2017;6:1-23.
59. Engineer A, Saiyin T, Greco ER, Feng Q. Say NO to ROS: their roles in embryonic heart development and pathogenesis of congenital heart defects in maternal diabetes. *Antioxidants*. 2019;8:436.

60. Wang J, Ma H, Tong C, et al. Overnutrition and maternal obesity in sheep pregnancy alter the JNK-IRS-1 signaling cascades and cardiac function in the fetal heart. *FASEB J*. 2010;24:2066-2076.
61. Wang Q, Zhu C, Sun M,, et al. Maternal obesity impairs fetal cardiomyocyte contractile function in sheep. *FASEB J*. 2019;33:2587-2598.
62. Matafome P, Rodrigues T, Sena C, Seiça R. Methylglyoxal in Metabolic Disorders: Facts, Myths, and Promises. *Med Res Rev*. 2017;37:368-403.
63. Kalapos MP. Where does plasma methylglyoxal originate from? *Diabetes Res Clin Pract*. 2013;99:260-271.
64. Poulsen MW, Hedegaard RV, Andersen JM, et al. Advanced glycation endproducts in food and their effects on health. *Food Chem Toxicol*. 2013;60:10-37.
65. Allaman I, Bélanger M, Magistretti PJ. Methylglyoxal, the dark side of glycolysis. *Frontiers in Neuroscience*. 2015;9:23.
66. Yan SF, Ramasamy R, Schmidt AM. Receptor for AGE (RAGE) and its ligands-cast into leading roles in diabetes and the inflammatory response. *J Mol Med*. 2009;87:235-247.
67. Jones ML, Buhimschi IA, Zhao G, et al. Acute Glucose Load, Inflammation, Oxidative Stress, Nonenzymatic Glycation, and Screening for Gestational Diabetes. *Reprod Sci*. 2020;27(8):1587-1594. http://dx.doi.org/10.1007/s43032-020-00188-5
68. Li S, Yang H. Relationship between advanced glycation end products and gestational diabetes mellitus. *J Matern Neonatal Med*. 2019;32:2783-2789.
69. Li H, Dong A, Lv X. Advanced glycation end products and adipocytokines and oxidative stress in placental tissues of pregnant women with gestational diabetes mellitus. *Exp Ther Med*. 2019;18:685.
70. Rajaraman B, Ramadas N, Krishnasamy S,, et al. Hyperglycaemia cause vascular inflammation through advanced glycation end products/early growth response-1 axis in gestational diabetes mellitus. *Mol Cell Biochem*. 2019;456:179-190.
71. Konishi H, Nakatsuka M, Chekir C, et al. Advanced glycation end products induce secretion of chemokines and apoptosis in human first trimester trophoblasts. *Hum Reprod*. 2004;19:2156-2162.
72. Chiavaroli V, D'Adamo E, Giannini C, et al. Serum levels of receptors for advanced glycation end products in normal-weight and obese children born small and large for gestational age. *Diabetes Care*. 2012;35:1361-1363.
73. Roest PAM, Molin DGM, Schalkwijk CG, et al. Specific local cardiovascular changes of n ε-(carboxymethyl) lysine, vascular endothelial growth factor, and smad2 in the developing embryos coincide with maternal diabetes-induced congenital heart defects. *Diabetes*. 2009;58:1222-1228.
74. Kawaharada R, Masuda H, Chen Z,, et al. Intrauterine hyperglycemia-induced inflammatory signalling via the receptor for advanced glycation end products in the cardiac muscle of the infants of diabetic mother rats. *Eur J Nutr*. 2018;57:2701-2712.
75. Chandna AR, Kuhlmann N, Bryce CA, et al. Chronic maternal hyperglycemia induced during mid-pregnancy in rats increases RAGE expression, augments hippocampal excitability, and alters behavior of the offspring. *Neuroscience*. 2015;303:241-260.
76. Yang G, Cancino GI, Zahr SK, et al. A Glo1-methylglyoxal pathway that is perturbed in maternal diabetes regulates embryonic and adult neural stem cell pools in murine offspring. *Cell Rep*. 2016;17:1022-1036.
77. Ejdesjö A, Brings S, Fleming T, Fred RG, Nawroth PP, Eriksson UJ Receptor for advanced glycation end products (RAGE) knockout reduces fetal dysmorphogenesis in murine diabetic pregnancy. *Reprod Toxicol*. 2016;62:62-70.
78. Takeuchi M, Takino J-I, Furuno S, et al. Assessment of the concentrations of various advanced glycation end-products in beverages and foods that are commonly consumed in Japan. *PLoS One*. 2015;10:e0118652.
79. Mericq V, Piccardo C, Cai W, et al. Maternally transmitted and food-derived glycotoxins: a factor preconditioning the young to diabetes? *Diabetes Care*. 2010;33:2232-2237.
80. Amezcua-Prieto C, Martínez-Galiano J, Cano-Ibáñez N, et al. Types of carbohydrates intake during pregnancy and frequency of a small for gestational age newborn: A case-control study. *Nutrients*. 2019;11:523.
81. Dale MTG, Magnus P, Leirgul E, et al. Intake of sucrose-sweetened soft beverages during pregnancy and risk of congenital heart defects (CHD) in offspring: a Norwegian pregnancy cohort study. *Eur J Epidemiol*. 2019;34:383-396.
82. Mullie P, Clarys P. Consumption of artificially sweetened beverages during pregnancy is associated with a twofold higher risk of infant being overweight at 1 year. *Evidence-Based Nursing*. 2017;20:11.
83. Csongová M, Gurecká R, Koborová I, et al. The effects of a maternal advanced glycation end product-rich diet on somatic features, reflex ontogeny and metabolic parameters of offspring mice. *Food Funct*. 2018;9:3432-3446.
84. Toop CR, Muhlhausler BS, O'Dea K, Gentili S. Impact of perinatal exposure to sucrose or high fructose corn syrup (HFCS-55) on adiposity and hepatic lipid composition in rat offspring. *J Physiol*. 2017;595:4379-4398.
85. Plagemann A, Harder T, Schellong K, Schulz S, Stupin JH. Early postnatal life as a critical time window for determination of long-term metabolic health. *Best Pract Res Clin Endocrinol Metab*. 2012;26:641-653.
86. Federico G, Gori M, Randazzo E, Vierucci F. Skin advanced glycation end-products evaluation in infants according to the type of feeding and mother's smoking habits. *SAGE Open Med*. 2016;4:205031211668212.
87. Schwarzenbolz U, Hofmann T, Sparmann N, Henle T. Free maillard reaction products in milk reflect nutritional intake of glycated proteins and can be used to distinguish 'organic' and 'conventionally' produced milk. *J Agric Food Chem*. 2016;64:5071-5078.
88. Francisco FA, Barella LP, Silveiria SS,, et al. Methylglyoxal treatment in lactating mothers leads to type 2 diabetes phenotype in male rat offspring at adulthood. *Eur J Nutr*. 2018;57:477-486.
89. Dittrich R, Hoffmann I, Stahl P, et al. Concentrations of Nε-carboxymethyllysine in human breast milk, infant formulas, and urine of infants. *J Agric Food Chem*. 2006;54:6924-6928.
90. Prosser CG, Carpenter EA, Hodgkinson AJ. N ε -carboxymethyllysine in nutritional milk formulas for infants. *Food Chem*. 2019;274:886-890.
91. Šebeková K, et al. Plasma concentration and urinary excretion of Nε- (carboxymethyl)lysine in breast milk- and formula-fed infants. In Annals of the New York Academy of Sciences. (Blackwell Publishing Inc.; 2008.
92. Hellwig M, Geissler S, Peto A, Knütter I, Brandsch M, Henle T. Transport of free and peptide-bound pyrraline at intestinal and renal epithelial cells. *J Agric Food Chem*. 2009;57:6474-6480.
93. Mark AB, Poulsen MW, Andersen S, et al. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. *Diabetes Care*. 2014;37:88-95.

94. De Courten B, de Courten MP, Soldatos G, et al. Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: a double-blind, randomized, crossover trial. *Am J Clin Nutr*. 2016;103:1426-1433.
95. Qu W, Yuan X, Zhao J, et al. Dietary advanced glycation end products modify gut microbial composition and partially increase colon permeability in rats. *Mol Nutr Food Res*. 2017;61(10):1700118 (1-14). http://dx.doi.org/10.1002/mnfr.201700118
96. Seiquer I, Rubio LA, Peinado MJ, Delgado-Andrade C, Navarro MP. Maillard reaction products modulate gut microbiota composition in adolescents. *Mol Nutr Food Res*. 2014;58:1552-1560.
97. Yacoub R, Nugent M, Cai W, et al. Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; A randomized open label controlled trial. *PLoS One*. 2017;12:e0184789.
98. Peters MA, Hudson PM, Jurgelske W. The acute toxicity of methylglyoxal in rats: The influence of age, sex, and pregnancy. *Ecotoxicol Environ Saf*. 1978;2:369-374.
99. Kutlu T. Dietary glycotoxins and infant formulas. *Turk Pediatri Arsivi*. 2016;51:179-185.
100. Elmhiri G, Mahmood DFD, Niquet-Leridon C, et al. Formula-derived advanced glycation end products are involved in the development of long-term inflammation and oxidative stress in kidney of IUGR piglets. *Mol Nutr Food Res*. 2015;59:939-947.
101. Firmin S, Elmhiri G, Crepin D, Souidi M, Taouis M, Abdennebi-Najar L. Formula derived Maillard reaction products in post-weaning intrauterine growth-restricted piglets induce developmental programming of hepatic oxidative stress independently of microRNA-21 and microRNA-155. *J Dev Orig Health Dis*. 2018;9:566-572.
102. Peppa M, He C, Hattori M, et al. Fetal or neonatal low-glycotoxin environment prevents autoimmune diabetes in NOD mice. *Diabetes*. 2003;52:1441-1448.
103. Shimizu I, Hiramatsu Y, Omori Y, Nakabayashi M. Comparison of HbA1c and glycated albumin as a control marker for newborn complications in diabetic women in a multicentre study in Japan (Japan glycated albumin study group: study 2). *Ann Clin Biochem*. 2018;55:639-646.
104. Jiménez-Chillarón JC, Nijland MJ, Ascensão AA, et al. Back to the future: Transgenerational transmission of xenobiotic-induced epigenetic remodeling. *Epigenetics*. 2015;10:259-273.
105. Gyllenhammer LE, Entringer S, Buss C, Wadhwa PD. Developmental programming of mitochondrial biology: a conceptual framework and review. *Proc Biol Sci*. 2020;287:20192713.
106. Mele J, Muralimanoharan S, Maloyan A, Myatt L. Impaired mitochondrial function in human placenta with increased maternal adiposity. *Am J Physiol - Endocrinol Metab*. 2014;307:E419-E425.
107. Ferey JLA, Boudoures AL, Reid M, et al. A maternal high-fat, high-sucrose diet induces transgenerational cardiac mitochondrial dysfunction independently of maternal mitochondrial inheritance. *Am J Physiol - Hear Circ Physiol*. 2019;316:H1202-H1210.
108. Shelley P, Martin-Gronert MS, Rowlerson A, et al. Altered skeletal muscle insulin signaling and mitochondrial complex II-III linked activity in adult offspring of obese mice. *Am J Physiol - Regul Integr Comp Physiol*. 2009;297:R675-R681.
109. Khamoui AV, Desai M, Ross MG, Rossiter HB. Sex-specific effects of maternal and postweaning high-fat diet on skeletal muscle mitochondrial respiration. *J Dev Orig Health Dis*. 2018;9:670-677.
110. Borengasser SJ, Lau F, Kang P,, et al. Maternal obesity during gestation impairs fatty acid oxidation and mitochondrial SIRT3 expression in rat offspring at weaning. *PLoS One*. 2011;6:e24068.
111. Cardenas-Perez RE, Fuentes-Mera L, de la Garza AL, et al. Maternal overnutrition by hypercaloric diets programs hypothalamic mitochondrial fusion and metabolic dysfunction in rat male offspring. *Nutr Metab*. 2018;15:38.
112. Nicholas LM, Nagao M, Kusinski LC, Fernandez-Twinn DS, Eliasson L, Ozanne SE Exposure to maternal obesity programs sex differences in pancreatic islets of the offspring in mice. *Diabetologia*. 2020;63:324-337.
113. Wang H, Chen Y, Mao X, Du M. Maternal obesity impairs fetal mitochondriogenesis and brown adipose tissue development partially via upregulation of miR-204-5p. *Biochim Biophys Acta - Mol Basis Dis*. 2019;1865:2706-2715.
114. Von Bergen NH, Koppenhafer SL, Spitz DR, et al. Fetal programming alters reactive oxygen species production in sheep cardiac mitochondria. *Clin Sci*. 2009;116:659-668.
115. Peterside IE, Selak MA, Simmons RA. Impaired oxidative phosphorylation in hepatic mitochondria in growth-retarded rats. *Am J Physiol - Endocrinol Metab*. 2003;285:1258-1266.
116. Bruin JE, Petre MA, Raha S, et al. Fetal and neonatal nicotine exposure in wistar rats causes progressive pancreatic mitochondrial damage and beta cell dysfunction. *PLoS One*. 2008;3:e3371.
117. Higami Y, Pugh TD, Page GP, Allison DB, Prolla TA, Weindruch R. Adipose tissue energy metabolism : altered gene expression profile of mice subjected to long-term caloric restriction. *FASEB J*. 2004;18:415-417.
118. McCurdy CE, Schenk S, Hetrick B, et al. Maternal obesity reduces oxidative capacity in fetal skeletal muscle of Japanese macaques. *JCI Insight*. 2016;1:1-17.
119. Mdaki KS, Larsen TD, Wachal AL, et al. Maternal high-fat diet impairs cardiac function in offspring of diabetic pregnancy through metabolic stress and mitochondrial dysfunction. *Am J Physiol - Hear Circ Physiol*. 2016;310:H681-H692.
120. Wesolowski SR, Kasmi KCE, Jonscher KR, Friedman JE. Developmental origins of NAFLD: a womb with a clue. *Nat Rev Gastroenterol Hepatol*. 2017;14:81-96.
121. Friedman JE. Developmental programming of obesity and diabetes in mouse, monkey, and man in 2018: Where Are We Headed ?. *Diabetes*. 2018;67:2137-2151.
122. Saben JL, Boudoures AL, Asghar Z, et al. Maternal Metabolic Syndrome Programs Mitochondrial Dysfunction via Germline Changes across Three Generations. *Cell Rep*. 2016;16:1-8.
123. Tarry-Adkins JL, Fernandez-Twinn DS, Chen JH, et al. Poor maternal nutrition and accelerated postnatal growth induces an accelerated aging phenotype and oxidative stress in skeletal muscle of male rats. *DMM Dis Model Mech*. 2016;9:1221-1229.
124. Rodríguez-Rodríguez P, Ramiro-Cortijo D, Reyes-Hernández CG, et al. Implication of oxidative stress in fetal programming of cardiovascular disease. *Front Physiol*. 2018;9:1-13.
125. Rashid CS, Bansal A, Simmons RA. Oxidative stress, intrauterine growth restriction, and developmental programming of type 2 diabetes. *Physiology*. 2018;33:348-359.
126. Fetterman JL, Pompilius M, Westbrook DG, et al. Developmental exposure to second-hand smoke increases adult atherogenesis and alters mitochondrial dna copy number and deletions in apoE-/- Mice. *PLoS One*. 2013;8:e66835.

127. Abraham M, Collins CA, Flewelling S, et al. Mitochondrial inefficiency in infants born to overweight African-American mothers. *Int J Obes*. 2018;42:1306-1316.
128. Kim J, Piao Y, Pak YK, et al. Umbilical cord mesenchymal stromal cells affected by gestational diabetes mellitus display premature aging and mitochondrial dysfunction. *Stem Cells Dev*. 2015;24:575-586.
129. Barnes SK, Ozanne SE. Pathways linking the early environment to long-term health and lifespan. *Prog Biophys Mol Biol*. 2011;106:323-336.
130. Alfaradhi MZ, Fernandez-Twinn DS, Martin-Gronert MS, et al. Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. *Am J Physiol Integr Comp Physiol*. 2014;307:R26-R34.
131. Huang Q, Wen X, Bai K-W, et al. Protective effects of leucine on redox status and mitochondrial-related gene abundance in the jejunum of intrauterine growth-retarded piglets during early weaning period. *Arch Anim Nutr*. 2017;71:93-107.
132. Rodríguez-González GL, Vega CC, Boeck L, et al. Maternal obesity and overnutrition increase oxidative stress in male rat offspring reproductive system and decrease fertility. *Int J Obes*. 2015;39:549-556.
133. Vega CC, Reyes-Castro LA, Bautista CJ,, et al. Exercise in obese female rats has beneficial effects on maternal and male and female offspring metabolism. *Int J Obes*. 2015;39:712-719.
134. Vega CC, Reyes-Castro LA, Rodríguez-González GL, et al. Resveratrol partially prevents oxidative stress and metabolic dysfunction in pregnant rats fed a low protein diet and their offspring. *J Physiol*. 2016;594:1483-1499.
135. Santos M, Rodríguez-González GL, Ibáñez C, et al. Adult exercise effects on oxidative stress and reproductive programming in male offspring of obese rats. *Am J Physiol - Regul Integr Comp Physiol*. 2015;308:R219-R225.
136. Stevanović-Silva J, Beleza J, Coxito P, et al. Maternal high-fat high-sucrose diet and gestational exercise modulate hepatic fat accumulation and liver mitochondrial respiratory capacity in mothers and male offspring. *Metabolism*. 2021;116:154704.
137. Şanlı E, Kabaran S. Maternal obesity, maternal overnutrition and fetal programming: effects of epigenetic mechanisms on the development of metabolic disorders. *Curr Genomics*. 2019;20:419-427.
138. Nathanielsz PW, Yan J, Green R, et al. Maternal obesity disrupts the methionine cycle in baboon pregnancy. *Physiol Rep*. 2015;3:e12564.
139. Aagaard-Tillery KM, Grove K, Bishop J, et al. Developmental origins of disease and determinants of chromatin structure: Maternal diet modifies the primate fetal epigenome. *J Mol Endocrinol*. 2008;41:91-102.
140. Wesolowski SR, Mulligan CM, Janssen RC, et al. Switching obese mothers to a healthy diet improves fetal hypoxemia, hepatic metabolites, and lipotoxicity in non-human primates. *Mol Metab*. 2018;18:25-41.
141. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. *Nature*. 2019;571:489-499.
142. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics (Review). *Oncol Rep*. 2017;37:3-9.
143. Weaver JR, Susiarjo M, Bartolomei MS. Imprinting and epigenetic changes in the early embryo. *Mamm Genome*. 2009;20:532-543.
144. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14:R115.
145. Caldji C, Hellstrom IC, Zhang TY, Diorio J, Meaney MJ. Environmental regulation of the neural epigenome. *FEBS Lett*. 2011;585:2049-2058.
146. Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. *J Nutrit*. 2007;137:223S-228S.
147. Schübeler D. Function and information content of DNA methylation. *Nature*. 2015;517:321-326.
148. Patil V, Ward RL, Hesson LB. The evidence for functional non-CpG methylation in mammalian cells. *Epigenetics*. 2014;9:823-828.
149. Pastor WA, Aravind L, Rao A. TETonic shift: biological roles of TET proteins in DNA demethylation and transcription. *Nat Rev Mol Cell Biol*. 2013;14:341-356.
150. Liberman N, Wang SY, Greer EL. Transgenerational epigenetic inheritance: from phenomena to molecular mechanisms. *Curr Opin Neurobiol*. 2019;59:189-206.
151. Matilainen O, Quirós PM, Auwerx J. Mitochondria and epigenetics - crosstalk in homeostasis and stress. *Trends Cell Biol*. 2017;27:453-463.
152. Xu W, Yang H, Liu Y, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell*. 2011;19:17-30.
153. Menzies KJ, Zhang H, Katsyuba E, Auwerx J. Protein acetylation in metabolism-metabolites and cofactors. *Nature Rev Endocrinol*. 2016;12:43-60.
154. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. *Cold Spring Harb Perspect Biol*. 2014;6:a018713.
155. Pietrocola F, Galluzzi L, Bravo-San Pedro JM, Madeo F, Kroemer G. Acetyl coenzyme A: a central metabolite and second messenger. *Cell Metab*. 2015;21:805-821.
156. Imai SI, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. *Nature*. 2000;403:795-800.
157. Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab*. 2019;29:1028-1044.
158. Mihaylova M, Vasquez D, Ravnskjaer K, et al. Class IIa histone deacetylases are hormone-activated regulators of FOXO and mammalian glucose homeostasis. *Cell*. 2011;145:607-621.
159. Ferrari A, Fiorino E, Giudici M, et al. Linking epigenetics to lipid metabolism: focus on histone deacetylases. *Mol Membr Biol*. 2012;29:257-266.
160. Knutson SK, Chyla BJ, Amann JM, Bhaskara S, Huppert SS, Hiebert SW Liver-specific deletion of histone deacetylase 3 disrupts metabolic transcriptional networks. *EMBO J*. 2008;27:1017-1028.
161. Kirchner H, Osler ME, Krook A, Zierath JR. Epigenetic flexibility in metabolic regulation: disease cause and prevention? *Trends Cell Biol*. 2013;23:203-209.
162. Czubryt MP, McAnally J, Fishman GI, Olson EN. Regulation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and mitochondrial function by MEF2 and HDAC5. *Proc Natl Acad Sci USA*. 2003;100:1711-1716.
163. Gao Z, Yin J, Zhang J, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes*. 2009;58:1509-1517.
164. Feng D, Liu T, Sun Z, et al. A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. *Science (80-.)*. 2011;331:1315-1319.

165. Raychaudhuri N, Raychaudhuri S, Thamotharan M, Devaskar SU. Histone code modifications repress glucose transporter 4 expression in the intrauterine growth-restricted offspring. *J Biol Chem*. 2008;283:13611-13626.
166. Herrera E. Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. *Eur J Clin Nutr*. 2000;54:S47-S51.
167. Teperino R, Schoonjans K, Auwerx J. Histone methyl transferases and demethylases; Can they link metabolism and transcription? *Cell Metab*. 2010;12:321-327.
168. Ducker GS, Rabinowitz JD. One-carbon metabolism in health and disease. *Cell Metab*. 2017;25:27-42.
169. He S, Owen DR, Jelinsky SA, Lin LL. Lysine methyltransferase SETD7 (SET7/9) regulates ROS signaling through mitochondria and NFE2L2/ARE pathway. *Sci Rep*. 2015;5:14368.
170. Ge K. Epigenetic regulation of adipogenesis by histone methylation. *Biochim Biophys Acta - Gene Regulat Mech*. 2012;1819:727-732.
171. Desai M, Jellyman JK, Ross MG. Epigenomics, gestational programming and risk of metabolic syndrome. *Int J Obes*. 2015;39:633-641.
172. Yang Q-Y, Liang J-F, Rogers CJ, et al. Maternal obesity induces epigenetic modifications to facilitate Zfp423 expression and enhance adipogenic differentiation in fetal mice. *Diabetes*. 2013;62:3727-3735.
173. Borengasser SJ, Zhong Y, Kang P, et al. Maternal obesity enhances white adipose tissue differentiation and alters genome-scale DNA methylation in male rat offspring. *Endocrinology*. 2013;154:4113-4125.
174. Matilainen O, Quirós PM, Auwerx J. Mitochondria and epigenetics – crosstalk in homeostasis and stress. *Trends Cell Biol*. 2017;27:453-463.
175. Quirós PM, Mottis A, Auwerx J. Mitonuclear communication in homeostasis and stress. *Nat Rev Mol Cell Biol*. 2016;17:213-226.
176. Couvillion MT, Soto IC, Shipkovenska G, Churchman LS. Synchronized mitochondrial and cytosolic translation programs. *Nature*. 2016;533:499-503.
177. Richter-Dennerlein R, Oeljeklaus S, Lorenzi I, et al. Mitochondrial protein synthesis adapts to influx of nuclear-encoded protein. *Cell*. 2016;167:471.e10-483.e10.
178. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci USA*. 2008;105:17046-17049.
179. Tobi EW, Lumey LH, Talens RP, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet*. 2009;18:4046-4053.
180. Tobi EW, Heijmans BT, Kremer D, et al. DNA methylation of IGF2, GNASAS, INSIGF and LEP and being born small for gestational age. *Epigenetics*. 2011;6:171-176.
181. Filiberto AC, Maccani MA, Koestler DC, et al. Birthweight is associated with DNA promoter methylation of the glucocorticoid receptor in human placenta. *Epigenetics*. 2011;6:566-572.
182. El Hajj N, Pliushch G, Schneider E, et al. Metabolic programming of MEST DNA methylation by intrauterine exposure to gestational diabetes mellitus. *Diabetes*. 2013;62:1320-1328.
183. Busada JT, Cidlowski JA. Mechanisms of Glucocorticoid Action During Development. Current Topics in Developmental Biology vol. 125 (Elsevier Inc., 2017).
184. Jimeno B, Hau M, Gómez-Díaz E, Verhulst S. Developmental conditions modulate DNA methylation at the glucocorticoid receptor gene with cascading effects on expression and corticosterone levels in zebra finches. *Sci Rep*. 2019;9:1-11.
185. Nijland MJ, Mitsuya K, Li C, et al. Epigenetic modification of fetal baboon hepatic phosphoenolpyruvate carboxykinase following exposure to moderately reduced nutrient availability. *J Physiol*. 2010;588:1349-1359.
186. Zhu P, Wang W, Zuo R, Sun K. Mechanisms for establishment of the placental glucocorticoid barrier, a guard for life. *Cell Mol Life Sci*. 2019;76:13-26.
187. Jung C, Ho JT, Torpy DJ, et al. A longitudinal study of plasma and urinary cortisol in pregnancy and postpartum. *J Clin Endocrinol Metab*. 2011;96:1533-1540.
188. Ghnenis AB, Odhiambo JF, Smith AM, Pankey CL, Nathanielsz PW, Fordl SP A heretical view: rather than a solely placental protective function, placental 11ß hydroxysteroid dehydrogenase 2 also provides substrate for fetal peripheral cortisol synthesis in obese pregnant ewes. *J Dev Orig Health Dis*. 2021;12:94-100.
189. Smith AM, Pankey CL, Odhiambo JF, Ghnenis AB, Nathanielsz PW, Ford SP. Rapid communication: reduced maternal nutrition during early-to mid-gestation elevates newborn lamb plasma cortisol concentrations and eliminates the neonatal leptin surge. *J Anim Sci*. 2018;96:2640-2645.
190. Fletcher AJW, Forhead AJ, Fowden AL, et al. Effects of gestational age and cortisol treatment on ovine fetal heart function in a novel biventricular Langendorff preparation. *J Physiol*. 2005;562:493-505.
191. Tuersunjiang N, Odhiambo JF, Shasa DR, et al. Maternal obesity programs reduced leptin signaling in the pituitary and altered GH/IGF1 axis function leading to increased adiposity in adult sheep offspring. *PLoS One*. 2017;12:e0181795.
192. Li C, Jenkins S, Huber HF, Nathanielsz PW. Effect of maternal baboon (Papio sp.) dietary mismatch in pregnancy and lactation on post-natal offspring early life phenotype. *J Med Primatol*. 2019;48:226-235.
193. Wyrwoll CS, Seckl JR, Holmes MC. Altered placental function of 11β-hydroxysteroid dehydrogenase 2 knockout mice. *Endocrinology*. 2009;150:1287-1293.
194. Dy J, Guan H, Sampath-Kumar R, Richardson BS, Yang K. Placental 11β-Hydroxysteroid Dehydrogenase Type 2 is reduced in pregnancies complicated with idiopathic intrauterine growth restriction: evidence that this is associated with an attenuated ratio of cortisone to cortisol in the umbilical artery. *Placenta*. 2008;29:193-200.
195. Gómez-Roig MD, Mazarico E, Cárdenas D, et al. Placental 11B-Hydroxysteroid Dehydrogenase Type 2 mRNA levels in intrauterine growth restriction versus small-for-gestational-age fetuses. *Fetal Diagn Ther*. 2016;39:147-151.
196. Maniam J, Antoniadis C, Morris MJ. Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. *Front. Endocrinol. (Lausanne)*. 2014;5:1-17.
197. Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J Clin Invest*. 1998;101:2174-2181.
198. Cleasby ME, Kelly PAT, Walker BR, Seckl JR. Programming of rat muscle and fat metabolism by in utero overexposure to glucocorticoids. *Endocrinology*. 2003;144:999-1007.
199. Kelly BA, Lewandowski AJ, Worton SA, et al. Antenatal glucocorticoid exposure and long-term alterations in aortic function and glucose metabolism. *Pediatrics*. 2012;129.

200. Tamashiro KLK, Moran TH. Perinatal environment and its influences on metabolic programming of offspring. *Physiol Behav*. 2010;100:560-566.
201. Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change: the lancet commission report. *Lancet*. 2019;393:791-846.
202. Jellyman JK, Martin-Gronert MS, Cripps RL, et al. Effects of cortisol and dexamethasone on insulin signalling pathways in skeletal muscle of the ovine fetus during late gestation. *PLoS One*. 2012;7:1-7.
203. Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, Burdge GC Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPARα promoter of the offspring. *Br J Nutr*. 2008;100:278-282.
204. Takaya J, Iharada A, Okihana H, Kaneko K. A calcium-deficient diet in pregnant, nursing rats induces hypomethylation of specific cytosines in the 11β-hydroxysteroid dehydrogenase-1 promoter in pup liver. *Nutr Res*. 2013;33:961-970.
205. Stevens A, Begum G, Cook A, et al. Epigenetic changes in the hypothalamic proopiomelanocortin and glucocorticoid receptor genes in the ovine fetus after periconceptional undernutrition. *Endocrinology*. 2010;151:3652-3664.
206. Drake AJ, McPherson RC, Godfrey KM, et al. An unbalanced maternal diet in pregnancy associates with offspring epigenetic changes in genes controlling glucocorticoid action and foetal growth. *Clin Endocrinol (Oxf)*. 2012;77:808-815.

How to cite this article: Grilo LF, Tocantins C, Diniz MS, et al. Metabolic Disease Programming: From Mitochondria to Epigenetics, Glucocorticoid Signalling and Beyond. *Eur J Clin Invest*. 2021;00:e13625. https://doi.org/10.1111/eci.13625