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Review on intrauterine programming: Consequences in rodent models of mild diabetes and mild fat overfeeding are not mild

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ABSTRACT

An adverse intrauterine programming occurs in diabetes and obesity as the consequence of an adverse maternal environment that affects the appropriate fetoplacental development and growth. Experimental models of diabetes and fat overfeeding have provided relevant tools to address putative mechanisms of the adverse intrauterine programming. The current knowledge far extends from the original thoughts of the resulting intrauterine programming of metabolic and cardiovascular diseases to a full range of alterations that affect multiple tissues, organs, and systems that will compromise the long-life health of the offspring. This review examines the postnatal effects of rodent models of mild diabetes and fat overfeeding, identifying the multiple organ derangements in the offspring resulting from mild maternal adverse conditions. In addition, the comparison of experimental models of severe diabetes and fat overfeeding and the crucial role of the placenta are discussed, providing an update of the actual scenario of the putative mechanisms and adverse consequences of maternal metabolic derangements.

1. Introduction

The incidence of metabolic diseases is increasing worldwide, and the intrauterine programming is clearly involved in this increase [1,2]. Barker et al. were the first in developing the concept of intrauterine programming, identifying the relationship of adverse fetal growth outcomes and adult diseases [3]. Although the concept of intrauterine programming was initially described in relationship to famine and growth restriction, it was rapidly extended to be linked to macrosomia, the other extreme of the adverse fetal growth, an adverse outcome that is clearly associated with maternal diabetes and fat overfeeding [4–6]. Currently, the concept of intrauterine programming is wide and complex and refers to the ability of an adverse exposure during development to cause changes in the physiology, metabolism, and/or epigenome of an individual, which will lead to an increased risk of disease in their later life [7]. This concept includes changes originating at different developmental windows, and changes resulting from a disturbance at the cellular, tissue, or organ level that can be either adaptive or not in the intrauterine milieu but lead to adverse effects in a postnatal situation [7,8].

In diabetes, the intrauterine programming of metabolic diseases in the offspring's later life is evidenced in type 1, type 2, and gestational diabetic pregnancies, and human studies have identified nongenetic causes for this adverse programming [9–11]. Accordingly, nongenetic causes of intrauterine programming of offspring diseases are clearly evidenced in chemically induced experimental models of diabetes [12,13]. In dietary fat overfeeding, a main cause of overweight and obesity, it is clear that intrauterine programming of offspring diseases can be generated under different genetic backgrounds, despite different periods of the administration of the fat diet [14–16].

Aiming to illustrate the capacity of minor disturbances to affect the offspring's later life, this review addresses intrauterine programming in the offspring of experimental models of mild diabetes and mild fat overfeeding, evaluated mainly in rodents. In addition, a comparison of the adverse outcomes in mild or more severe conditions is addressed. Finally, the role of the placenta as a major player in determining the intrauterine programming is considered.

2. Intrauterine programming in experimental models of mild diabetes

Traditionally, pathogenic mechanisms underlying hyperglycemia have been evidenced in *in vitro* experiments carried out in the presence of glucose concentrations over 15 mM. Similarly, fasting blood glucose values in most experimental models of diabetes, induced either chemically or genetically, are higher than 15 mM. In reproductive studies, these high blood glucose levels often lead to embryo or fetal loss [12]. Thus, those diabetic animals in which pregnancy is achieved became experimental models useful to analyze the impact of maternal diabetes on the first stages of development, resorption, and malformation rates, and allowed to gain insights into the mechanisms of induction of these alterations [12,17,18]. On the other hand, sustaining pregnancy until term under these levels of hyperglycemia

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has become a larger challenge, and different approaches, including the induction of diabetes by administration of chemicals in the already pregnant animals and/or partially controlling the hyperglycemia with insulin, have been used to bypass this problem [12].

In these experimental models of severe diabetes, fetal growth retardation and reduced neonatal weight are mostly observed. These adverse outcomes may also be observed in poorly controlled diabetic women and are associated with the intrauterine programming of metabolic and cardiovascular diseases [12,19]. On the other extreme of fetal growth impairments, macrosomia is the most common adverse outcome in human diabetic pregnancies, a hallmark highly associated with altered programming of metabolic and cardiovascular diseases [6,20]. In parallel, macrosomia is the most frequent outcome in mild experimental models of diabetes [19,21,22]. This section examines the evidence of adverse intrauterine programming in mild diabetes experimental models (blood glucose values below 15 mM), as the outcomes and mechanisms involved may be more closely related to that observed in human diabetic pregnancies, and thus may further facilitate translational approaches from basic science to clinical medicine in the field of diabetes and pregnancy. Of note, in many rodent strains, healthy pregnant animals show blood glucose values around 5–6.5 mM, and thus, only values over 6.7 mM are used to diagnose diabetes. Fasting glycemia values in healthy rats can be higher than those in healthy women (in which normal glycemia values are up to 5.1–5.5 mM according to the diagnostic criteria). Thus, mild glycemia values in rats may be higher than those considered mild in humans, and caution should be taken when translating these results to humans.

2.1. Intrauterine programming of alterations in glucose metabolism

Experimental models of mild diabetes, induced either genetically or chemically, have convincingly demonstrated a disturbed metabolism in the offspring. In genetic models, it is important to differentiate those genetic alterations that will lead to diabetes in the offspring and the effects of the intrauterine programming. Embryo transfer experiments in Goto Kakizaki (GK) rats, a genetic model of diabetes with blood glucose values around 7 mM, have shown hyperglycemia and glucose intolerance in the adult offspring when wild-type embryos are transferred to GK female recipients, evidencing the intrauterine programming of the diabetic disease [23].

The chemical models of diabetes allow evaluating intrauterine effects under a wild-type genetic background. The degree of hyperglycemia induced by streptozotocin is dependent on the exquisite regulation of the pancreatic β-cell death/survival pathways; thus, variations in the strain, housing and/or diet are as important as the route of administration and dose [11,12]. This implies that the indicated dose/route of administration of streptozotocin may result in different blood glucose values among different settings. Therefore, rather than the dose administered when comparing different settings, the resulting blood glucose values are the values that will define the mildness or severity of the model.

Studies in mild diabetic rats have identified that the adult offspring (diabetes induced by a low dose of streptozotocin administration (30 mg/kg i.v) on day 1 of gestation; maternal fasting blood glucose values around 10 mM) shows decreased insulin responses and impaired glucose tolerance as well as morphological alterations in the endocrine pancreas [24,25]. The adult macrosomic offspring from diabetic rats (diabetes induced by streptozotocin administration (37 mg/kg i.p.) on day 5 of gestation; maternal fasting blood glucose values around 10 mM) show abnormal glucose tolerance and insulin response curves as well as reduced ^{14}C-glucose conversion to triglycerides in adipocytes [26].

Pregestational mild diabetes induced in rat neonates by streptozotocin administration (90 mg/kg s.c.; fasting blood glucose values around 11 mM) causes increased fasting glycemia and insulinemia in the adult offspring, which is evident from the fifth month of age in both males and females [27]. Indicating a link between gestational diabetes mellitus (GDM) and the future development of type 2 diabetes, gestational diabetes is induced in 3-month-old female offspring from these mild diabetic rats when mated with control males [28].

Altogether, the evidence shows intrauterine programming of diabetes in the offspring of mild diabetic rodents when diabetes is induced either before and during pregnancy, denoting the compromised metabolism due to the adverse development of the fetus exposed to mild maternal hyperglycemia.

2.2. Intrauterine programming of alterations in lipid metabolism

The importance of altered lipid metabolism in the induction of complications of the diabetic disease is now clearly recognized not only in nonpregnant patients but also in diabetic pregnancies and offspring's diseases [5,29]. Alterations in the offspring's lipid metabolism and deposition are studied in both chemically induced and genetic experimental models of mild diabetes. The db/+ mouse is a model of gestational diabetes, as these mice are not diabetic prior to gestation. The genetic defect is a heterozygous loss-of-function mutation in the leptin receptor gene that leads in the pregnant mice to impaired glucose tolerance and insulin responses [30,31]. In this model, comparing wild-type offspring (+/+ born to db/+ females mated with +/+ males) with controls (+/+ born to control dams), it is clear that the altered intrauterine environment leads to impaired glucose tolerance and increases in body weight and adipocyte size, as well as increased leptin and apelin serum concentrations in the adult offspring [32].

In the streptozotocin-induced neonatal model of mild diabetes (90 mg/kg s.c., maternal blood glucose values around 11 mM), not only the mothers have increased circulating lipids during pregnancy, but also the fetuses accumulate lipids in different organs including the liver, the lungs, and the heart [33–35]. Interestingly, the adult male and female offspring of these mild diabetic rats show increased triglycerides circulating levels, suggesting intrauterine programming of lipid metabolic disbalances [27]. Although the mechanisms involved remain unclear, it is interesting that treatments during gestation with olive oil (treatments with antioxidant capacity and ability to activate the peroxisome proliferator activated receptor (PPAR) pathway) prevent the increased triglyceridemia in the adult offspring [27].

Macrosomic male newborn offspring from diabetic rats (diabetes induced by streptozotocin administration on day 5 of pregnancy (40 mg/kg i.p.); maternal blood glucose values around 15 mM) show increased levels of circulating triglycerides and cholesterol as well as increased liver lipid content [21,36]. At 2 and 3 months of age, these offspring also present increased body weight, increased adipocyte size, and increased lipoperoxidation in erythrocytes [21,26]. Dietary treatments enriched in eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-tocopherol from the pre-pregnancy state and until the offspring's adulthood reduces body weight, serum triglycerides, cholesterol, and lipoperoxidation. The amelioration of the pro-oxidant state is also evidenced by the upregulation of antioxidant enzymes and the increase in plasma total antioxidant status [36]. Accumulation of epididymal adipose tissue, reduced adiponectin, and increased expression of pro-inflammatory genes (CD14, CD68, and TLR-2) in this adipose tissue are found in the adult male offspring of

diabetic mice (diabetes induced by multiple doses of streptozotocin during pregnancy (day 5–10, 40 mg/kg i.v.); blood glucose values of the pregnant mice around 10 mM) [37]. Altogether, these data imply a clear relationship between oxidative stress and lipid alterations in fetuses and offspring, and that lipid metabolic impairments are intrauterinely programmed in the offspring of mild diabetic mothers.

2.3. Intrauterine programming of blood pressure and renal alterations

Seven-day-old offspring of mild diabetic rats (diabetes induced by neonatal streptozotocin administration, 50 mg/kg i.p.) show a reduced number of nephrons together with a renal accumulation of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, suggesting reduced nitric oxide bioavailability [38].

In a rat model induced by streptozotocin (25 mg/kg i.p.) on day 1 of pregnancy (maternal blood glucose levels around 13 mM), hypertension is evidenced in the adult male offspring of diabetic rats either fed or not fed with a high salt diet. The offspring weight and the renal weight are increased in the diabetic group, although there are no differences in the nephron number. In addition, alterations in renal function are suggested by increased levels of creatinine in urine. In addition, *N*-acetyl-β-D-glucosaminidase, a marker of tubular cell disturbances, is also increased in the urine of adult offspring of these mild diabetic rats [39].

2.4. Intrauterine programming of heart alterations

Cardiac alterations, closely associated with the metabolic and blood pressure alterations, have been found to be programmed in the offspring from experimental models of mild diabetes. The heart rate is reduced in 3–4-month-old male offspring from mild diabetic rats (diabetes induced by streptozotocin on day 1 of gestation (25 mg/dl i.p.); maternal blood glucose values around 13 mM), an alteration that seems to be compensated at 5 months of age [39]. On the other hand, increased nitric oxide production, a marker of the pro-inflammatory state is evidenced in the heart of 5-month-old offspring of mild diabetic rats (diabetes induced by neonatal streptozotocin administration (90 mg/kg s.c.); maternal blood glucose values around 11 mM). In addition, the heart of female and male offspring of these diabetic rats accumulates different lipid species and shows increased lipoperoxidation [27]. The results obtained by supplementing mild diabetic mothers with olive oil, a diet that provides polyphenols and PPAR activators and prevents the increased lipid accumulation and lipoperoxidation in the heart of adult male and female offspring, provide insights into the relevance of the pro-oxidant environment as a mechanism underlying intrauterine programming [27].

Overall, animal studies demonstrated that mild maternal diabetes provides developmental origins of adult cardiac alterations, which together with the evidenced changes in metabolic parameters and the renal alterations, demonstrate their capacity to program metabolic and cardiovascular diseases in the adult.

2.5. Comparison with intrauterine programming in experimental models of severe diabetes

Experimental studies in rodents with blood glucose values over 15 mM during pregnancy usually show increased resorption and malformation rates and alterations in fetal development [12,17]. In addition, in commonality with mild models of diabetes, the capacity to induce intrauterine programming of metabolic alterations has been evidenced [11,13]. Indeed, as examples, in studies in which diabetes was induced by steptozotocin administration on day 1 of pregnancy, achieving maternal blood glucose values around 20 mM, the fetal weight is reduced and the weanling offspring show altered orexigenic and anorexigenic responses, probably involved in the insulin resistance and increased body weight shown in the adult offspring [40,41]. Increased body weight and adipose tissue accumulation and dysfunction are also evidenced in adult male offspring of an experimental model obtained by steptozotocin administration to 5-day-old rats (120 mg/kg i.p.) leading to blood glucose levels over 20 mM [42].

Hypertension, kidney morphological alterations, and reduced vascular reactivity in mesenteric arteries are observed in the adult offspring from diabetic rats (diabetes induced by streptozotocin (35 or 45 mg/kg i.p.) on day 0 of pregnancy; blood glucose values around 20 mM) [38,43]. Cardiac function is altered in the adult offspring of diabetic rats obtained by streptozotocin administration during pregnancy (day 1 of pregnancy, 35 mg/kg i.p., glucose values around 26 mM [44] and day 12 of pregnancy, 50 mg/kg i.p., treated with insulin to maintain glucose levels between 11 and 22 mM [45]).

Therefore, animal models of both mild and severe diabetes convincingly demonstrate adverse intrauterine programming of metabolic, cardiac, and vascular impairments. Despite differences in the degree of severity, more marked in the severe diabetic models, the close similarity of the systems affected in mild and severe diabetic experimental models suggests either a commonality of pathological mechanisms induced *in utero* or reciprocal actions resulting from the *in utero* adaptations to the adverse maternal metabolic/pro-oxidant environment [5,7,8]. Overall, this implies that fetal development is susceptible to mild and nonmild maternal metabolic changes. As the placenta is the maternal-fetal interphase, a fundamental role of the placenta in the intrauterine programming of diseases is warranted.

2.6. The role of the placenta in diabetes-induced intrauterine programming

The placenta, an essential organ for fetal development, is increasingly recognized as a relevant player in intrauterine programming [46,47]. In human pregnancies, the size, shape, the transport and endocrine function, as well as the pro-inflammatory and pro-oxidant state of the placenta have been associated not only with the fetal well-being but also with the offspring's long-term health [48–50].

Animal models of diabetes have provided evidence of placental alterations linked to alterations in fetal development and weight, alterations related to the fetal outcome [12]. In experimental models of severe diabetes (blood glucose values over 15 mM), which often show altered fetal and placental weight, the placenta shows impaired remodeling during development, structural alterations, accumulation of glycogen and lipids, increased oxidative stress, and increased apoptosis [51–56].

In experimental models of mild diabetes (blood glucose values lower than 15 mM), in which fetal weight and placental weight are frequently increased, the placenta shows increased lipid deposition, increased matrix metalloproteinase expression and activity, overproduction of nitric oxide, peroxynitrite-induced damage, and reduced mitochondrial function [50,57–60]. As mild diabetic models that lead to intrauterine programming show impaired metabolic and pro-oxidant/pro-inflammatory alterations in the placenta, it is likely that impairments in the fetus derived from placental alterations are key players in the intrauterine programming of diseases. Moreover, mild diabetes leads to increased oxidative and nitrative stress, as well as to increased mammalian target of rapamycin (mTOR) signaling in the placenta in their pregnant female offspring that develop GDM, suggesting intrauterine programming of placental alterations in the next gen-

eration [28]. Further research in GDM models will be of value to analyze putative changes in the placenta that may be present prior to GDM diagnosis.

Experimental difficulties occur when attempting to attribute to the placenta a main role as an inductor of adverse intrauterine programming. Indeed, fetal development and placental development and function are tightly coordinated to result in a healthy outcome. Thus, alterations and compensations originating in either the fetal or placental compartments because of adverse maternal, fetal, and placental conditions will be closely interrelated and involved in the genesis of the adverse intrauterine programming. On the other hand, the solid evidence of alterations originating in embryo, fetal and offspring's health in maternal diabetes suggests a crucial role of the placenta exposed to mild and nonmild diabetes in the intrauterine programming of diseases.

In this sense, interventions that prevent alterations in the offspring of mild diabetic rats, such as maternal treatments enriched in unsaturated fatty acids that activate PPARs, are also found to be beneficial to the fetus and the placenta [33,34,57,61,62]. Nevertheless, caution should be taken when translating these results to humans. Human studies showed reduced transfer, increased utilization, and/or increased oxidation of PUFAs in maternal diabetes [63,64]. Moreover, PUFAs supplementation in diabetic and obese pregnant women reduces serum, placental or adipose tissue pro-oxidant/pro-inflammatory markers [63,65]. On the other hand, various studies performed in healthy pregnant women have failed to show the beneficial effect of PUFAs supplementation in preventing adverse perinatal outcomes [66]. Thus, although there is a clear consensus that PUFAs should be provided in sufficiency during gestation, the appropriate amounts required by a pregnant diabetic woman through gestation and the amounts that may induce a benefit in the outcome remain unknown [29,64].

The three isoforms of the nuclear receptors PPARs have a relevant role in the control of placental development, metabolism, and pro-inflammatory state [67–69]. Maternal diabetes induces changes in PPAR pathways [70]. PPARγ and PPARα have been found reduced in the placenta of mild experimental models of diabetes and of a newly developed model of GDM induced by intrauterine programming [28,61,71]. Similar reductions have also been found in the placenta of diabetic patients and in trophoblast cells isolated from GDM patients [70,72,73]. The epigenetic regulation of PPARs is involved in the intrauterine programming of diseases, as evidenced in different animal models [68]. Studies performed in women have shown increased methylation of the PPARα promoter gene and increased expression of miR-519d, a predicted regulator of PPARα mRNA translation, in GDM placentas, alterations possibly related to the decreased expression of PPARα [74,75]. Although several works have identified oxidative stress and altered nutrients and metabolites as putative inducers of PPAR epigenetic modifications [68,76,77], and although markers of oxidative stress are evident in the placenta in mild experimental models of diabetes [50,57], further work is needed to elucidate the stimulus that leads to impaired PPAR epigenetic changes in the placenta in maternal diabetes. In addition, higher methylation of PPARγ coactivator 1 alpha (PGC-1α) promoter has been observed in the placenta from GDM patients and correlated with increased cord blood leptin concentrations [78]. As many different epigenetic changes are induced in the placenta in different pathological conditions, including GDM, further studies in the field are expected to improve our understanding of the precise role of the placenta in ruling the future health of the offspring [79–81].

2.7. Limitations

Despite the usefulness of mild models of diabetes to understand maternal diabetes-induced damage and its postnatal consequences, it is important to point out that there are various limitations. First, it is known that streptozotocin administration mediates β-cell destruction through a pro-oxidant/pro-inflammatory process, and that there is a release of the stored insulin when β-cells are destructed [12]. Thus, although this short-time process would not affect studies in nonpregnant animals, it may be relevant in models in which streptozotocin is given during pregnancy.

On the other hand, depending on the time at which the streptozotocin is administered, not only the short impact resulting from the drug administration, but also, more importantly, the impact of the impaired maternal metabolism will occur at different developmental stages and thus may have a different impact on the offspring. The fact that an adverse programming is evidenced in models of mild diabetes obtained under streptozotocin administration either preconceptionally or at different times of gestation suggests a whole pregnancy susceptibility to changes induced in the intrauterine life that would affect the offspring's later life.

Finally, another limitation in most models of mild diabetes in rodents is that animals are lean. As both diabetes and obesity are prevalent diseases and lead to an adverse intrauterine programming, an update on mild models of fat overfeeding will follow, as this is important to understand similarities and differences with that observed in experimental models of mild diabetes and pregnancy.

3. Intrauterine programming in experimental models of mild fat overfeeding

Maternal overnutrition and/or obesity are associated with anomalies that range from increased lipemia to cardiovascular alterations, fatty liver, obesity, glucose intolerance, and other disturbances that affect their life and the life of their offspring [82–84].

Researchers have used different approaches to achieve models of maternal overnutrition that lead to maternal obesity/overweight, useful to study the effects and possible causes and mechanisms of the programming of metabolic impairments in the offspring [14,85–87]. Seeking for a good experimental model of overnutrition, companies and researchers have designed different mixtures of nutrients, manipulating dietary fat as the main source of energy. Commercial diets offer a wide range of diets with different percentages and types of fat. Self-made diets combine regular chow with fat (saturated fat) from animal source (butter or lard). Another self-made option, called cafeteria diet, consists of a western-like or junk food diet that offers distinct sources of fast-hypercaloric food, such as snacks, chocolate, cookies, and muffins among others. The use of these diets leads to the development of rodent models of fat overfeeding with different characteristics.

Of note, as maternal overfeeding leads to obesity, it is difficult to discriminate between the effects of an overload in a specific component of the diet and the effects of maternal obesity per se. There are experimental models of obesity induced by different infusion volumes of a liquid diet, which contains an equilibrated composition of each nutrient [86]. In these models, there is absence of an increased acquisition of energy from only one of the nutrient components, e.g., lipids. Nevertheless, these models still present overnutrition tightly combined to obesity.

Cafeteria diets mimic human poor eating habits, but their composition is difficult to evaluate because of the too many different

sources on different days, which makes the experiments hard to reproduce. In addition, the presence of high concentrations of salt makes a model that is not simply a model of overnutrition because high salt per se has its own effects on maternal and fetal metabolism [88]. To provide optimal nutrition, regular rodent diets have between 10% and 15% calories from fat [89]. Therefore, to induce obesity/overweight in a short period of time and before the reproductive period is over, researchers and companies use diets with high percentage of fat. High fat diets (HFDs) contain between 30% and 60% calories from fat, principally saturated fat. A HFD with 60% calories from fat (HFD60) induces a dramatic increase in body weight, which can reach 50% in some models [90–92] and may also induce GDM [16]. Aiming to analyze mild changes in maternal weight and metabolism, a very commonly used HFD is the commercial one with 45% of fat (HFD45). Comparative studies showed that HFD45 induces an increase in weight and fat mass together with many metabolic derangements similar, although not so pronounced, to those observed in cafeteria- and HFD60-treated animals [90,91,93]. Diets with nearly 30% of fat (HFD30) are also useful to induce slight increases in maternal body weight and fat mass [91,94]. Similar outcomes are observed when feeding animals with commercial or self-made diets that do not overpass 50% of calories from fat, which induce an increase of 17–27% in maternal weight [95–97].

Considering all this for the purpose of this review, we will define models of mild fat overfeeding as those achieved by feeding rodents with diets in which fat provides between 30% and 50% of the calories. Importantly, models of mild fat overfeeding can be achieved by offering the fatty diet prior to gestation, during gestation, lactation, after weaning or a combination of these. In addition, as the diet can be provided at different time frames prior to pregnancy, the time span of exposure to the fatty diet varies in each model. Besides, each model may vary in the species, strain, and the way of breeding, leading to a variable genetic background. Moreover, there are different types of diet regarding fat content and the fat origin, generating differences in lipid moieties and fatty acid saturation grade.

Despite these many sources of variability, studies in the available models have shown many similar adverse outcomes in the offspring. This section focuses on the effects of mild fat overfeeding on the programming of metabolic and/or functional disturbances in the rodent offspring.

3.1. Intrauterine programming of alterations in adipose tissue in experimental models of mild fat overfeeding

One would expect that models from fat overfeeding would present an increase in weight not only in the mothers but also in the fetuses and the offspring. However, regarding fetal weight, divergent outcomes characterize experimental models of mild fat overfeeding. Both an increase in body weight in term fetuses from Wistar rats fed HFD47 [95] and a decrease in neonatal body weight in Wistar rats fed a commercial HFD45 have been reported [98]. In contrast, offspring from C57BL/6 mice fed HFD49 shows no changes in birth weight [96,99]. Despite these discrepancies, most reports indicate that the offspring from experimental models of mild fat overfeeding shows a significant increase in weight at weaning [14,96–99]. Later, these offspring show either no changes [14,97] or a further increase in body weight [98–102]. Different outcomes in weight are not apparently explained by the species, strain, percent or source of fat, or time or frame of exposure to the diet. A combination of all these factors might be interacting to induce different placental alterations/adaptations that make an impact on fetal growth as will be discussed later. The weight of weanlings is influenced by the high concentrations of lipids in maternal milk. The weight of the adult offspring, after receiving regular chow, will vary depending on the programming of metabolic health resulting from the interrelationship between the maternal influence and the intrinsic characteristics of the offspring.

Many studies report increases in circulating levels of lipids in fetuses, neonates, and weanlings [14,95,97,100]. However, after lactation, when the exposure to the maternal diet ends and the pup eats regular chow, different models show different outcomes. Increased lipemias have been shown in suckling and adult offspring from rats fed with HFD50 and the adult offspring from mice fed HFD45 [100,103], while no changes have been reported in the adult offspring of rats fed with HFD47 or HFD45 [14,101]. Besides high circulating levels of free fatty acids and triacylglycerols, increased levels of insulin and leptin as well as insulin resistance have been shown in the adult offspring from models of fat overfeeding [97,98,100].

Obesity is characterized by an increase in fat deposition in adipose tissue and/or other tissues. Adipose tissue from different locations, measured as weight or by DEXA studies, is increased in suckling and late offspring from rodent models of mild fat overfeeding [97–99,104]. In addition, adipose tissue from adult offspring presents an increase in adipocyte diameter, pro-inflammatory markers, and clear indicators of pro-inflammatory macrophage infiltration, anomalies involved in the development of insulin resistance [97,103]. Transgenerational experiments have shown that along four generations of HFD35 feeding, the adipose tissue develops an increase in adipocyte diameter, which cannot be completely abolished by offering a low fat diet to this fourth offspring [104]. From the outcomes observed in the offspring from models of mild fat overfeeding, it is clear that the alterations observed in the programming of adipose tissue can lead to general inflammation and insulin resistance, alterations that are clearly linked to the development of the metabolic syndrome.

3.2. Intrauterine programming of alterations in the endothelial/cardiovascular system in experimental models of mild fat overfeeding

Maternal obesity/overweight leads to cardiovascular alterations in the offspring [84]. Offspring from rodent models fed diets with almost 45 calories from fat shows an increase in blood pressure from post-natal day 80 to post-natal week 36 either with [101] or without sex dependence [103,105,106]. Samuelsson and coworkers showed that the offspring from mild fat-overfed rats develop hypertension in basal or stressful conditions at 30 days of age [106]. These pups become hypertensive before they become obese and hyperleptinemic at 90 days of age, when hypertension persists [106]. Endothelial dysfunction has also been reported in mesenteric arteries and aortic rings in the adult offspring from rodents fed with diets with approximately 40–47 calories from fat [101,105,107]. In addition, female and male offspring from these rats show an altered aortic structure [107].

Few studies have addressed sex-dependent alterations in the endothelial and/or cardiovascular system in response to maternal fat overfeeding. In the adult offspring from mild fat overfed rats, Armitage and coworkers found aortic anomalies without sexual dimorphic effects [107]. Nevertheless, they found alterations in the renal structure and enzymes activity only in males [107]. Khan et al. found some sex-dependent effects in the adult offspring from mild fat overfed rats that received regular chow from weaning to adulthood. Females developed hypertension, differently from males, which showed no blood-pressure alterations, although they developed hyperglycemia and decreased heart rate, pointing out the relevance of sexual dimorphism in the programming of cardiac alterations [105]. In a rodent model of severe fat overfeeding, Xue et al. found several

cardiac alterations only in male adult offspring, showing altered systolic function, renin-angiotensin system, and ischemia-reperfusion response [108]. Although it seems that maternal severe fat overfeeding programs sex-dependent anomalies more markedly in the offspring cardiovascular system than maternal mild fat overfeeding, further research is needed to clarify this point.

The programming of cardiovascular and endothelial dysfunction evidenced by the reports cited points out the importance of maternal metabolic control because a moderate increase in fat in the diet of the mother may shorten the life expectancy of the offspring.

3.3. Intrauterine programming of alterations in muscle in experimental models of mild fat overfeeding

Obesity is characterized not only by an increase in fat mass but also by altered lean mass. Increased lipid accumulation/adipocyte infiltration in muscle is a hallmark of obesity and is a main cause for muscle insulin resistance and dysfunction. Suckling pups from rats fed a HFD35 have more fat mass and more muscle mass (tibialis and soleus), although their muscles show a decrease in glucose transporter 4 (Glut4) and myogenic differentiation protein (myoD) expression [109]. However, after eating a control rat chow, adult offspring show no increase in fat pad or muscle weight but still a decrease in Glut4, myoD, and myogenin expression in their muscles [110]. In addition, adult offspring from mild fat-overfed rats show reduced expression of the insulin cascade proteins [111]. Insulin resistance-related anomalies are therefore very common outcomes in the offspring from models of mild fat overfeeding. Female and male offspring from a similar rat model display clear indicators of an increase in lipid oxidation in their muscles at weaning and at 70 days of age. Interestingly, this increase in lipid oxidation is uncoupled of the mitochondrial respiratory chain, an alteration that leads to inefficient energy production and generates oxidative tissue damage [112]. Thus, the muscle alterations observed in the offspring of models of mild fat overfeeding challenge the muscular activity of this offspring and may lead to insulin resistance and an increased production of reactive oxygen species, predisposing them to several pathologies.

3.4. Intrauterine programming of alterations in appetite-satiety regulation circuits in experimental models of mild fat overfeeding

The central regulation of appetite, satiety, and energy expenditure is a key aspect when analyzing possible causes of obesity development. These circuits begin their building from early embryonic days and in rodents continue after delivery during the suckling period [113,114]. The offspring from rats fed a diet with 50% of calories from fat is obese at 70 days of age, with high circulating levels of lipids, leptin, and insulin [100]. During lactation, on post-natal day 15, the pups show an increase in the expression of many orexigenic peptides, both in the paraventricular nucleus (PVN) and in the parafornical lateral hypothalamus (PFLH). Conversely, the expression of these orexigenic peptides is observed to be downregulated in the arcuate nucleus (ARC) [100]. Elucidating the first steps of these events, Chang and coworkers showed increased neurogenesis of the orexigenic peptides-expressing neurons in the PVN and PFLH of the offspring at birth. Interestingly, they also reported increased neurogenesis and neurodifferentiation in the hypothalamic area on embryonic day 14, providing a potential clue in the investigation of the hypothalamic impairments observed in the offspring from obese mothers [100]. Chen and collaborators also reported that a mild overload of fat in maternal diet induces a basal decrease in the Y neuropeptide (NPY) in the ARC of 9-week-old offspring [115].

Leptin pathway impairments have been studied and reported by different authors. Leptin levels are increased not only in plasma but also in milk from lactating dams [116]. The suckling offspring from rats fed a HFD50 show an impaired expression of the main components of the satiety-appetite circuit in the ARC [15]. Leptin receptor long isoform (ObRb), NPY, signal transducer and activator of transcription 3 (STAT3), and Agouti related-peptide (Agrp) are downregulated, while suppressor of cytokine signaling-3 (SOCS3) is upregulated, suggesting central leptin resistance. Consistently, leptin-induced STAT3 phosphorylation is diminished in hyperphagic weanlings. Despite all this, normal food intake and hypothalamic signaling are restored in the 12-week-old offspring after regular chow eating [15]. Differently, Franco and coworkers showed hyperphagia, hyperleptinemia, and obesity at weaning and on the post-natal day 180, suggesting that leptin resistance persists later in the offspring's life [117,118]. Overall, mild fat overfeeding-induced anomalies in the system that control the appetite can lead or not lead to hyperphagia, exacerbating the predisposition to develop an obese phenotype induced by the maternal environment.

3.5. Intrauterine programming of alterations in the liver in experimental models of mild fat overfeeding

The liver is a target organ of diets enriched in fat content, and perinatal exposure to fatty diets is related to the development of nonalcoholic-fatty liver disease (NAFLD) in the offspring [83]. Changes in liver weight, possibly related to lipid overaccumulation/inflammation, are studied in experimental models of mild fat overfeeding. Neonatal and fetal liver weight is reported unchanged in rats fed a diet with a mild increase in fat [95,119]. Immediately after lactation, pups show either an increase [14,119,120] or a decrease in liver weight [121]. Later, adult offspring can also show either an increase [99] or no changes in liver weight [14]. Importantly, offspring from models of mild fat overfeeding show an increase in liver lipid accumulation that is not necessarily linked to liver weight in neonates [96,119], weanlings [14,119], and late offspring [14,99]. In association with lipid overaccumulation, the offspring from models of mild fat overfeeding shows increased liver expression of lipogenic genes and decreased expression of genes involved in lipid catabolism at different ages [14,96,99,122]. Another common alteration induced in the liver of the offspring by maternal mild fat diet is oxidative stress [14]. This is probably related to mitochondrial dysfunction, which is in turn related to an altered expression of genes involved in the generation of pro-oxidant molecules, respiratory chain function, and antioxidant capacity [96,123]. Finally, some authors have shown some signs of liver steatosis, with increased lipid accumulation and tissue vacuolization but without macrophage infiltration in the adult offspring from mild fat overfed mothers [99,122–124]. The degree of damage in the liver of the offspring from mild fat overfeeding rodents is not enough to define a nonalcoholic steatotic liver (NASH) but to define NAFLD. Because the liver is a key organ for metabolic control, programmed alterations in its function would compromise the function of other organs and systems and would be involved in the induction of metabolic syndrome in the offspring.

3.6. Comparison with intrauterine programming in experimental models of severe fat overfeeding

Severe fat overfeeding, which is here considered over 50% of calories from fat, induces a large increase in maternal weight that can reach a 50% increase previous and during pregnancy and lactation in some models and is accompanied by an increase in fat mass

[92,125,126]. In addition, mothers fed a severe fat overload commonly show hyperinsulinemia and hyperleptinemia [16,126–128]. These alterations were also observed in models of mild fat overfeeding [95,129]. However, differently from most models of mild fat overfeeding, a severe fat overload can also induce maternal glucose intolerance [125,130], increased fasting glucose levels [128], or GDM [16].

On the other hand, similar to the models of mild fat overfeeding, fetuses in rodent models of severe fat overfeeding can be either heavier or lighter than the corresponding controls and can show increased fat mass and circulating levels of blood glucose and insulin [92,125,128,130]. Later, weanlings mostly show an increase in weight and fat mass [126,131]. In addition, adult offspring from these models of severe fat overfeeding is mostly heavier and has increased body fat mass [126,132], a common outcome in offspring from models of mild fat overfeeding [130,133].

Similar to the offspring from models of mild fat overfeeding, hyperleptinemia, glucose intolerance, and insulin resistance are observed in the offspring of rodents fed HFD60 or HFD65 at different ages [126,130,134]. In addition, the offspring from HFD60-fed dams shows fasting hyperglycemia when born to mothers that had developed GDM [16,132]. The adipose tissue from early and late offspring of dams fed HFD60 shows increased adipocyte size, inflammation markers, macrophage infiltration indicators, and upregulated expression of genes involved in adipogenesis, lipogenesis, and regulators of lipid droplet size [128,135], similar to the outcomes observed in the models of mild fat overfeeding. However, offspring from both models of mild and severe fat overfeeding develop hypertension [101,132,133]. Cardiac alterations are evidenced in the male offspring from severe models of fat overfeeding [108] and in models from mild fat overfeeding [105].

Sex-dependent effects are found in the offspring from mild and severe fat overfeeding, although the mechanisms involved in the induction of these changes have not yet been clarified. Dahlhoff and coworkers found that adult male offspring develop increased weight, body fat, insulin and leptin levels and have a pronounced positive response in mRNA levels of genes involved in adipogenesis and lipogenesis in the liver. On the other hand, females display no changes in weight, decreased fat mass, increased glucose levels, and an altered expression of genes involved in fat mass expansion, lipid droplet size regulation, and apoptosis in their adipose tissue [130]. Differently, Elahi et al. showed increased weight and body fat only in adult female offspring from a mild model of fat overfeeding [124].

Regarding the appetite–satiety system, both severe and mild fat overfeeding models lead to similar impairments. Fetuses from female mice fed a HFD60 show alterations in the proliferation, apoptosis, and differentiation rate in the hippocampus, cortical ventral nucleus, and dentate gyrus neurons [92]. In addition, hyperinsulinemic and hyperleptinemic fetuses from HFD60 fed rats show upregulated expression of AgRP, NPY, POMC, ObRb, and other orexigenic genes involved in insulin and leptin central signaling pathways [127]. Moreover, central leptin resistance has been observed in the adult offspring of HFD65 fed dams [135], outcomes similar to those observed in the models of mild fat overfeeding.

Liver weight is shown to be decreased in the newborns from HFD60 fed rodents, together with increased indicators of inflammation, and triglyceride content [136], an outcome consistent with the increased fetal liver expression of lipogenesis genes shown by Qiao and collaborators [137]. On the other hand, increased liver weight, upregulation of the expression of the pro-adipogenic genes, and clear signs of steatosis are reported in 5-month old female offspring from HFD60 fed mice [130]. Molecular changes in both mild and severe fat overfeeding models are similar, although the steatosis degree is apparently more severe when programmed by mothers fed with a HF60 diet [130].

In summary, alterations in models of mild and overt fat overfeeding show similar but not equal outcomes. Importantly, severe fat overload can lead to GDM [16]. Impairments in adipose tissue are evidenced earlier, and the degree of liver damage is more severe in models of severe fat overfeeding than in models of mild fat overfeeding [130]. However, when studying programmed alterations in the late offspring (5–12 months), the outcomes are similar. Experiments are difficult to reproduce due to the wide variety of species, strain, and breeding conditions. Nevertheless, from the current reports in models of fat overfeeding, it is clearly concluded that either a mild or a severe overload of fat in the maternal diet leads to programmed metabolic disturbances in the offspring. The role of the placenta in this adverse outcome is discussed in Section 3.7.

3.7. The role of the placenta in the intrauterine programming of alterations in experimental models of fat overfeeding

The placenta is the organ that communicates the fetuses with their mothers, providing nutrients, water, oxygen, and other necessary substances to meet fetal demands of development and growth. Moreover, fetal undesirable excretion products are eliminated through the placental exchange to maternal circulation. Therefore, the ability of the placenta to successfully adapt to the maternal environment and fulfill fetal requests is linked to proper fetal growth and development. Newborn size and weight are clear indicators of future life quality and expectancy [82,138–140]. Placental efficiency is the ratio between fetal and placental weight, the latter being linked to the placental size and the exchange area. The maternal environments of mild fat overfeeding models are rich in circulating lipids and very commonly in hormones like insulin and leptin, both of them clear promoters of placental growth [141,142]. An increase in placental size is very likely related to an increase in nutrient transport to the fetus and consequently to fetal overgrowth. However, experimental models of mild fat overfeeding show a wide range of placental and fetal sizes. Indeed, fetal and/or neonatal growth is restricted in connection with placental insufficiency in rodents fed with diets with a moderate increase in fat, linked to impairments in fetal lung development [143,144]. In addition, fetal growth restriction is associated with diminished placental weight from rats fed a diet with 45% of calories from fat [145]. On the other hand, Heerwagen and collaborators showed unchanged fetal weight, increased placental weight, and placental insufficiency in mice fed with a moderate increase in fat, and the offspring from these animals develop obesity later in life [146]. Differently, fetal overgrowth is observed in mice and rat fed with diets with 32%, 41%, and 46% of calories from fat without alterations in placental weight or efficiency [129,147–149]. In addition, fetal and placental weight is enhanced without impairments in placental efficiency in a rat model of mild fat overfeeding whose offspring display no obesity but fatty liver at 140 days of age [14,95]. This suggests that the increased bioavailability of lipids does not necessarily lead to placental or fetal overgrowth. Independently of the percent of dietary lipids and the time of exposure, maternal fat overfeeding induces placental and fetal alterations, not always reflected in placental and/or fetal overweight, and the offspring from these mothers show many altered metabolic pathways [145,146,150]. It seems that increased lipid availability pushes the placenta to adapt/respond to such increase by changing its shape [151], vasculature [144], redox status, and/or antioxidant capacity, finally affecting the fetus metabolic programming [5]. Fetuses will in turn respond to placental adaptations, and the response will

depend on fetal genetics and will change fetal epigenetics, settling the bases for the programming of the future metabolic regulation. Searching for a link between the maternal hyperlipidemic environment and the fetal alterations that could lead to metabolic impairments in the offspring, many researchers have assessed the role of specific transporters as putative regulators.

Placental nutrient transport is highly dependent on the expression and activity of specific transporters. The expression and activity of lipid, glucose, and amino acid transporters are under the control of hormones like insulin or leptin and other nutrients [152]. Therefore, it is very likely that nutrient transport is increased in placentas immersed in maternal obese environments. Indeed, similarly to that observed in mild fat overfeeding, placental weight in models of overt fat overfeeding can be found either unchanged, increased or decreased in combination with different outcomes in fetal weight [16,125,153,154]. The gene expression of nutrient transporters is increased in placentas from HFD60-fed rodents that show increased fetal weight and fetal fat mass [137]. Epigenetic alterations are observed in placentas from models of overt fat overfeeding. Panchenko and collaborators showed an altered expression of the genes involved in epigenetic mechanisms, especially of the components of the histone-acetylation machinery in the placenta, probably linked to the fetal growth restriction observed in a model of HFD60 fed mice [125].

Sexual dimorphism has been evidenced in placentas from models of severe fat overfeeding. A diet highly enriched in fat (54%) exacerbates the sex dimorphism in gene expression of term placenta, being the females more susceptible to diet-induced upregulation [155] In addition, a HFD60 led to global DNA hypomethylation only in the female placenta and the differential methylation of clusters of imprinted genes important in the control of metabolic and physiological functions [154]. Maternal mild fat overfeeding also leads to sex-dependent placental alterations: a HFD45 induced decreased female fetal weight and decreased placental expression of TNFα and CD68. Differently, males showed increased placental expression of TNFα and nutrient transporters and no changes in fetal weight [145]. Further research is needed to clarify whether the sexual dimorphic effects depend on the percent of fat from the maternal diet.

Although maternal glycemia is not increased in mild models of fat overfeeding, fetuses from HFD41-and HFD46-fed mothers show increased glucose circulating levels either linked or not linked to an increased placental expression of glucose transporters (Glut-1 and Glut-3) [95,149]. Mice fed a HFD32 induce either no changes in the expression of placental glucose transporters [148] or increased expression and activity of Glut1 [147], while rats fed a HFD45 also show increased expression of Glut 1 and Glut 4 [145]. Amino acid transport is also increased in placentas from mild models of fat overfeeding [145,147]. Indeed, SNAT 2 expression and activity are increased in mice and rats fed a moderate overload of fat in maternal diet [145,147,149]. Related to this increase, mTORC1 pathways are activated and likely to be involved in fetal overgrowth [129,149]. An HFD45 model develops high circulating levels of lipids and, linked to this, an increase in placental expression of lipoprotein lipase (LPL) and CD36 [145]. Placental and/or fetal liver lipid content is increased probably because of an increase in lipid circulating levels and in the expression and/or activity of placental LPL. Later, offspring from this model develops obesity and fatty liver [95,146].

Disturbed placental structure, with altered thickness of decidua, junction zone, and labyrinth layer is observed, together with clear markers of placental and fetal inflammation, in mice and rats fed a HFD45 [145,156]. Linked to placental insufficiency, with or without fetal growth restriction, increased pro-inflammatory cytokines and macrophage infiltration are observed in placentas, fetuses and offspring from mild models of fat overfeeding [143,146]. Also linked to placental insufficiency, Lin and coworkers showed increased markers of oxidative stress-related tissue damage and decreased antioxidant capacity in placentas and the heart from fetuses of rats fed with a moderate increase in dietary fat [150]. Hayes and collaborators showed that a HFD45 induces placental insufficiency, linked to fetal growth restriction and increased resorption rates, probably related to placental hypoxia and pro-oxidant placental damage. Interestingly, vascularization is impaired in term placentas from these rats [144]. Investigations in early gestation of the same model have revealed that trophoblast invasion is increased in the mesometrial triangle, when the placenta is recently established, but decreased on embryonic day 18 (E18). Consequently, uterine spiral arteries are not invaded or remodeled on E18. These results suggest that an impaired blood flow in placentas and uteri is related to the fetal growth restriction observed in this model of mild fat overfeeding [144,157]. Similarly, placentas from severe fat overfeeding mice that present GDM show severe morphological alterations, including increased cellular fragmentation, fibrinonecrotic areas, number of dead endothelial cells, and decreased trophoblast number. These placentas also develop altered vascularization and increased lipoperoxidation, which lead to decreased placental weight and very likely to placental dysfunction [16]. Although the role of hyperglycemia in placental blood flow and endothelial dysfunction has been widely studied, further research is needed to clarify the role of lipids and/or lipotoxicity in the maternal-placental-fetal blood flow to improve the understanding of causes of fetal disturbances.

Overall, the role of the placenta in intrauterine programming of metabolic impairments would depend first on the success of placental blood flow establishment, tightly linked to placental efficiency. Impairments at this stage are likely to lead to fetal growth restriction, which programs metabolic derangements in the offspring's later life. When proper placental blood flow is achieved, increased nutrient transport to the fetus may lead to fetal overgrowth, which also programs metabolic disturbances in the offspring.

4. Conclusions

Investigations in rodent models of mild diabetes and mild fat overfeeding have allowed identifying mild adverse conditions as causes of intrauterine programming of alterations in multiple cell types, tissues, organs, and systems. The adverse outcome may be either a direct developmental derange/adaptative process resulting from the programming process or an effect resulting from an alteration in another system (e.g., a metabolic change) that will further affect a specific organ. Further works are needed to identify the precise nature of the adverse effects resulting from the intrauterine exposure to mild diabetes or mild fat overfeeding. As shown in Fig. 1, there are many common adverse outcomes evidenced in the offspring from animals with mild diabetes and mild fat overfeeding.

Of note, adverse intrauterine programming is evidenced both when mild diabetes is induced preconceptionally or during gestation and when mild fat overfeeding is administered at different times before or during gestation. This suggests that a series of diverse alterations occurring at different time windows in the mother, the placenta and the fetus can lead to the adverse postnatal outcome. Therefore, understanding the mechanisms involved in an adverse intrauterine programming is complex and still a challenge.

Although the complexity of the intrauterine development makes the current view really limited, the recognition of the importance of a proper maternal nutrition and metabolic balance and the relevance of the placenta to allow the appropriate fetal development needed for the

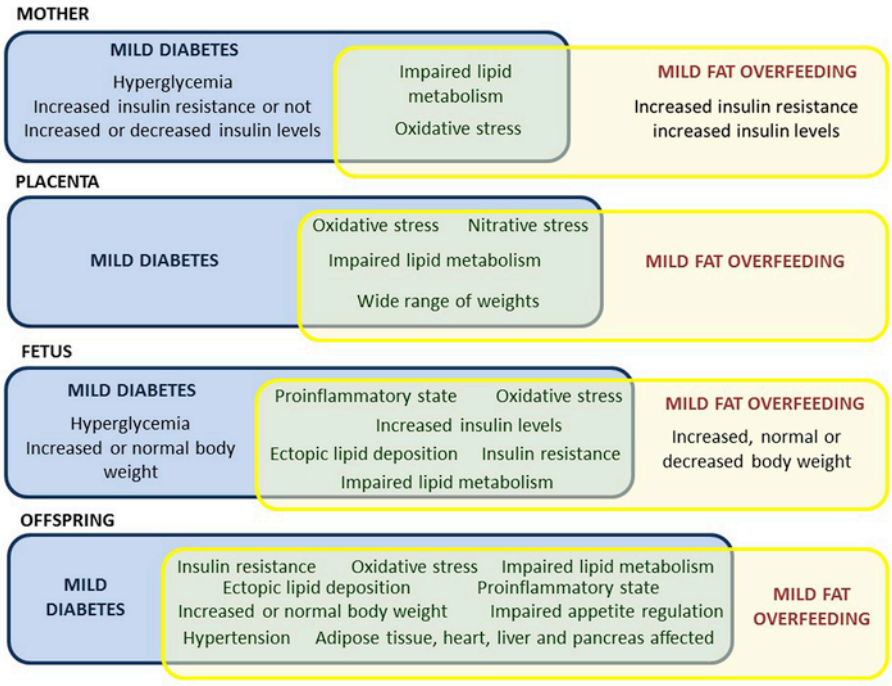

Fig. 1. Main common adverse outcomes in the mother, the placenta, the fetus, and the offspring in rodent models of mild diabetes and mild fat overfeeding. Maternal mild diabetes in blue, maternal mild diabetes overfeeding in yellow, and common outcomes in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

postnatal wellbeing as well as that mild impairments can lead to non-mild consequences, constitute a base that may help design translational approaches and provide opportunities to study early interventions to improve the health of our next generations.

Conflict of interest statement

We declare that we have no conflict of interest.

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