Placental Oxidative Stress

Schoots, Mirthe

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Chapter 7

REVIEW:
THE INFLUENCE OF THE DIETARY EXPOSOME ON OXIDATIVE STRESS IN PREGNANCY COMPLICATIONS

MH Schoots, JR Prins, JI Wessels, MJE Campmans-Kuijpers, GJ Navis, H van Goor, SA Robertson, EM van der Beek, L Sobrevia, SJ Gordijn

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Abstract

Pregnancy complications including fetal growth restriction, preeclampsia, and preterm birth, as well as gestational diabetes, affect one in every four to five pregnancies. Accumulating evidence indicates that increased production of reactive oxygen species accompanies these complications. Given that reactive oxygen species are cell stress-inducing agents, they may have a causal role in disease pathophysiology, although the exact mechanisms by which they contribute to pregnancy complications are not completely understood. Since many environmental and lifestyle factors and exposures are known to modulate reactive oxygen species production, the exposome of pregnant women could contribute to increased generation of reactive oxygen species. The objective of this review is to provide a comprehensive overview of the endogenous and exogenous exposome factors that regulate reactive species in healthy and complicated pregnancies. We also provide a description of dietary interventions aimed at the reduction of reactive species in order to attenuate adverse pregnancy outcome. Dietary interventions in general hold minimal risk in pregnancy and could therefore be considered a promising therapeutic approach.

Introduction

The perinatal period is of cardinal importance for the lifelong health of every individual. Suboptimal fetal circumstances encompass risk factors for developing chronic disease later in life. Diabetes, hypertension, stroke and coronary artery disease, for instance, have all been linked to suboptimal perinatal outcomes including placental malfunction. [1] Preeclampsia, fetal growth restriction (FGR), and preterm labor, common manifestations of the "great obstetrical syndromes", have common etiologies. [2] These conditions are each strongly linked to the growth and functional development of the placenta, and exhibit a long subclinical phase, becoming evident only when pregnancy progresses to the stage that the compensatory mechanisms can no longer be sustained. This subclinical phase provides a window of opportunity for potential interventions to protect against the later onset of overt symptoms.

The term "great obstetrical syndromes" (GOS) was first used to describe pregnancy-related disorders with a placental component as part of their etiology. GOS refers to preterm labor and premature rupture of membranes, preeclampsia, spontaneous pregnancy loss, stillbirth, and abnormal fetal growth. [2] GOS is steadily rising worldwide and around 15% of all pregnancies are complicated by GOS [3], most of them with a high recurrence risk. The overarching concept is that these etiologies arise from events during fetal development that impact the maternal-fetal exchange of nutrients, oxygen, waste products, and toxins; initiating subclinical pathology that progresses to clinical manifestation over the course of pregnancy. These events include exposure to endogenous metabolites along with exogenous nutrients, as the consequence of different exposome factors. The exposome is defined as the sum of all internal (endogenous) and external (exogenous) non-genetic factors that influence human health throughout life, including perinatal life. [4,5] These factors can be subdivided into three domains: (1) an internal domain (*endo*-exposome), for example hormones, inflammation and oxidative stress; (2) a specific external domain (*ecto*-exposome), for example infectious agents, diet and lifestyle; and (3) a general external domain that includes education, socio-economic status and mental burden. [5] During pregnancy the developing fetus is exposed to different *endo- and ecto-* exposome factors, most notably including oxidative stress, nutrition, and inflammation. [6,7] A particular example of a complication of pregnancy in which the exposome is involved is gestational diabetes mellitus (GDM). GDM is a metabolic disease in which the combination of maternal predisposition and placental factors results in progressively impaired glucose tolerance that becomes evident from the end of the second trimester to the third trimester of pregnancy. [8–10] GDM is a pathology where different *endo-*

and *ecto*-exposome factors disturb the maternal-fetal interaction (mainly through effects on the micro- and macrovascular endothelial function) resulting in negative consequences for the health of both the mother and the fetus with long-lasting postnatal sequelae. [7]

The pathogenesis underpinning each of the aforementioned pregnancy complications remains elusive, although a variety of predisposing factors, including a pre-pregnancy maternal body mass index (BMI) of at least 30 kg/m^2 and genetic predisposition, are recognized. [2] Both inflammation and excessive oxidative stress ¾imbalance between the production of reactive species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), and the antioxidant defense system¾ are strongly associated with the 'placental syndrome' that underpins the great obstetrical syndromes. [11,12] Placentation that is insufficiently deep results in maternal vascular malperfusion [13], secondary to increased oxidative stress associated with impaired maternal immune regulation. On the other hand, suboptimal placental invasion can itself lead to an earlier and less organized initial onset of blood flow in the placental intervillous spaces, also resulting in excessive oxidative stress. [14,15] Oxidative stress can thus have a significant role in both types of placental insufficiency due to abnormal remodeling of maternal vasculature and the resulting endothelial dysfunction. [12,16,17]

Oxidative stress and inflammation are closely related as inflammatory reactions cause oxidative stress and oxidative stress perpetuates an inflammatory response. [18] Inflammatory triggers that cause a shift from immune tolerance towards immune effector activation, and thus a harmful immune response, may result in reactions that can lead to increased oxidative stress and a higher risk of adverse pregnancy outcomes. [19]

The exact role of oxidative stress and inflammatory processes in both the onset and the progression of pregnancy complications remain unclear. However, the involvement of these processes in the pathology of GOS also provides promising therapeutic options. [12,20] Many *ecto*-exposome factors are known to influence oxidative stress pathways and inflammation, including dietary intake and (cessation of) smoking. [21] Options for pharmaceutical interventions during pregnancy are limited, as pharmaceutical companies are often reluctant to test medication in pregnant women. Dietary interventions carry only little risk in pregnancy, making dietary substrates a promising future therapeutic approach in pregnancy. [22] In investigating the effect of dietary substrates on pregnancy complications, a wide variety of dietary treatment options have been reported, ranging from changes in complete dietary patterns to single nutrients or mineral supplementations. It is also known that the immune response can be modulated by dietary intake. [23] As such, nutrition can be considered a strong candidate for a modifiable *ecto*-exposome factor that can be targeted in order to reduce oxidative stress and inflammation in pregnancy.

This narrative review summarizes current understanding of oxidative stress in pregnancy related to placental dysfunction and the potential for attenuating oxidative stress caused by *endo*- and *ecto*-exposome factors through dietary interventions.

EXPOSOME-INDUCED OXIDATIVE STRESS AND INFLAMMATION IN PREGNANCY

Oxidative stress in pregnancy

Oxidative stress itself should be regarded as an endogenous factor, belonging to the *endo*-exposome oxidative stress. [5] In broad terms, pregnancy is a physiological state of prolonged, mildly elevated oxidative stress due to the high oxygen metabolic need for fetal growth and development. [24] This mildly elevated oxidative stress is the result of physiological inflammatory phenomena of pregnancy that are required for the angiogenic processes needed to expand the placental vascular bed. [24]

Common oxygen-derived ROS and RNS products include superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}HO$), nitric oxide ($^{\bullet}NO$), and peroxynitrite ($ONOO^-$). Under physiological conditions, ROS and RNS play fundamental roles in cellular metabolism, cell signaling cascades, and the expression of genes. Increased metabolic activity of mitochondria in the placenta and over-generation of ROS induce oxidative stress during pregnancy. [17] ROS levels are negatively affected by several antioxidant enzymes that can be divided into two categories, namely, the enzymatic antioxidants superoxide dismutase (SOD), catalase (CAT), peroxiredoxin (Prx), and glutathione peroxidase (GPx), and the non-enzymatic antioxidants vitamin C, vitamin E, and glutathione (GSH). If this antioxidant capacity is not enough to scavenge the increased amount of ROS, oxidative stress leads to oxidative damage characterized by DNA- and protein damage and lipid peroxidation [17] (Figure 1).

ROS and RNS are generated continuously from various sources, and in healthy pregnancy they are eliminated by the feto-placental unit producing abundant corresponding antioxidants. [24] Under physiological conditions, cytotrophoblasts and villous stromal cells synthesize new antioxidants when exposed to ROS. Assuming that increased oxidative stress is of critical importance in the development of placental pathology, antioxidant therapy might be considered as a preventive therapeutic option. For example, several clinical studies have been conducted to investigate efficacy of strategies to improve the antioxidant capacity of pregnant women in an effort to reduce the risk of GDM. [25] This has been recently reviewed showing that dietary supplementation of vitamin D and myoinositol reduced the risk of GDM. [25]

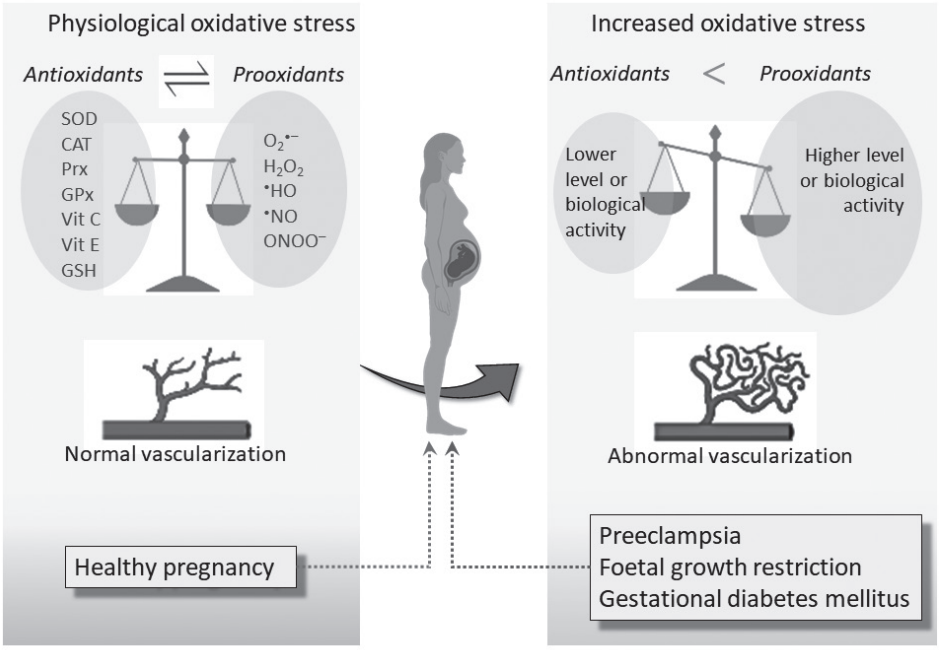

Figure 1. Increased oxidative stress and its consequences in pregnancy. Physiological oxidative stress is seen in pregnancy due to perturbation in the delicate balance between the availability and activity of antioxidants and pro-oxidants. In this physiological process, the normal metabolism in pregnancy generates several pro-oxidants, mainly reactive oxygen ($O_2^{\bullet-}$, H_2O_2, •HO) or nitrogen (•NO, $ONOO^-$) species. The biological production and activity of these species is regulated by antioxidant mechanisms, including enzymes (SOD, CAT, Prx, GPx) and micronutrients (vitamin C, vitamin E, GSH). The equilibrated state of oxidative stress allows normal uterine vascular adaptation and placental development, securing a healthy pregnancy. When the metabolic state of a pregnant woman is altered, the pro-oxidant generation and biological activity surpass the protective action of antioxidants. This phenomenon may be further changed due to reduced generation and biological activity of antioxidants. The result of this condition is dysregulated vascularization (*Abnormal vascularization*), resulting in diseases of pregnancy such as preeclampsia, gestational diabetes mellitus, and fetal growth restriction. $O_2^{\bullet-}$ superoxide anion, H_2O_2 hydrogen peroxide, •HO hydroxyl radical, •NO nitric oxide, $ONOO^-$ peroxynitrite, SOD superoxide dismutase, CAT catalase, Prx peroxiredoxin, GPx glutathione peroxidase, GSH glutathione.

Oxidative stress is measured in maternal blood and placental tissue by various indices. In maternal blood, malondialdehyde (MDA), the breakdown product of fatty acid oxidation, is an indicator of lipid peroxidation and of oxidative damage. MDA normally binds to thiobarbituric acid-reactive substances (TBARS) formed as a by-product of lipid peroxidation and is elevated in preeclampsia. In addition to the previously mentioned antioxidant enzymes, total antioxidant capacity and gasotransmitters are also used as indices. The antioxidant capacity in plasma can

be measured by the Ferric Reducing Ability of Plasma (FRAP) as a reflection of the oxidative stress status. [26] One of the best markers is free thiols, which have a strong predictive capacity. Plasma-free thiols have recently been shown to be significantly decreased in preeclampsia reflecting oxidative stress. [27,28] Therefore, a required level of thiols might be required to protect the mother and fetus from this hypertensive disorder. Other components of the *endo*-exposome are involved in the modulation of angiogenesis in the feto-placental unit by an equilibrium between pro- and anti-angiogenic factors. Fetal or placental pro-angiogenic factors that are detectable in the maternal blood include placental growth factor (PlGF) and heme oxygenase-1 (HO-1). Anti-angiogenic factors include soluble fms-like tyrosine kinase 1 (sFlt-1) and endoglin (ENG). Moreover, plasma markers of endothelial activation and placental dysfunction are the endo-exposome factors plasminogen-activator inhibitor 1 (PAI-1) and 2 (PAI-2). Finally, an increase in inflammation (*endo*-exposome) could contribute to oxidative stress, as pro-inflammatory cytokines are produced in response to ROS and subsequently stimulate further ROS production by target cells. [29]

Oxidative stress can be aggravated by a variety of *ecto*-exposome factors including environmental pollutants, lifestyle factors such as tobacco smoking, and the amount of dietary fat consumption. [30] Also, heavy metals consumed as environmental contaminants, such as arsenic, mercury, copper, and lead, are associated with higher oxidative stress increasing the risk of preeclampsia and preterm birth [31] and GDM. [7,32] Thus, adequate regulation of the inflammatory mediators and the *ecto*-exposome factors involved in triggering this state is essential for pregnancy success, and excessive ROS can perturb this.

Placental pathology associated with oxidative stress

The placental lesion most often related to oxidative stress and inflammation and the concurrent clinical conditions is maternal vascular malperfusion (MVM) (Figure 2). This lesion is characterized, among other things, by placental hypoplasia (low weight, maldevelopment), infarction, accelerated villous maturation, and decidual arteriopathy. [13] Due to impaired spiral artery remodeling, the oxygen tension in the placenta rises disproportionately, leading to a rise in ROS and eventually to oxidative stress. [12] Another common placental lesion, chronic villitis of unknown etiology, is often seen in (late) FGR (Figure 3 C-D). Due to a chronic lymphocytic CD8+ T cell infiltration of maternal origin the villi are damaged, thus reducing the amount of functional placental tissue available to participate in the exchange of oxygen and nutrients to the fetus. [13] In GDM, the placental parenchyma shows, in varying degree, delayed maturation with decreased number of vasculosyncytial membranes (Figure 3 A-B) [33]; thereby reducing the capacity of the placenta to deliver enough

nutrients and oxygen to the fetus and remove the necessary waste products. As a compensatory mechanism, the number of villous capillaries increases, known as chorangiosis [34] (Figure 3). However, the diffusion distance remains increased due to villous stromal proliferation. The increase in villous stromal cells and in villous capillaries results from disregulation of the glucose and oxygen metabolic pathways, although the exact mechanisms remain unclear. [35]

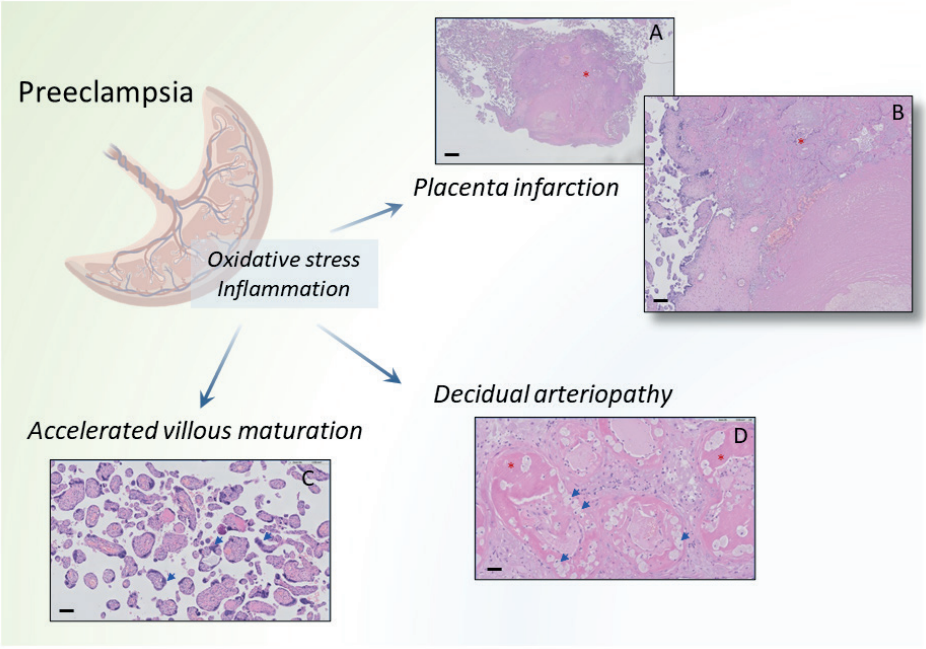

Figure 2. Histology of placental lesions in preeclampsia. Representative light microscope photographs of Hematoxylin/Eosin-stained placental samples. The excessive oxidative stress and inflammation in preeclampsia results in structural abnormalities in the placental vasculature leading to malperfusion. The most characteristics structural abnormalities include (A, B) placental infarction (*), (C) accelerated villous maturation with increased syncytial knotting (arrowheads), (D) decidual arteriopathy with necrosis of the vessel wall (*), and (E) presence and influx of foamy macrophages (arrowheads).

Inflammation in pregnancy

Inflammatory responses are also considered *endo*-exposome factors. The immune system plays a fundamental role in pregnancy. The principal role of the immune system is to protect against potentially dangerous microbial infections and tumor cells. In pregnancy the maternal immune system, however, faces a major challenge. The embryo and gestational tissues arising from the fusion of the male and female

gametes express both paternal and maternal major histocompatibility (MHC) antigens. Therefore, the fetus is semi-allogeneic to the maternal immune system. The maternal immune system must remain tolerant to the semi-allogeneic embryo and gestational tissue on the one hand and facilitate normal immune competence to protect against pathogens on the other hand. Adaptation of the maternal immune system during early pregnancy is therefore required in order to create an environment in which both immune tolerance and immune protection can coexist. [36,37]

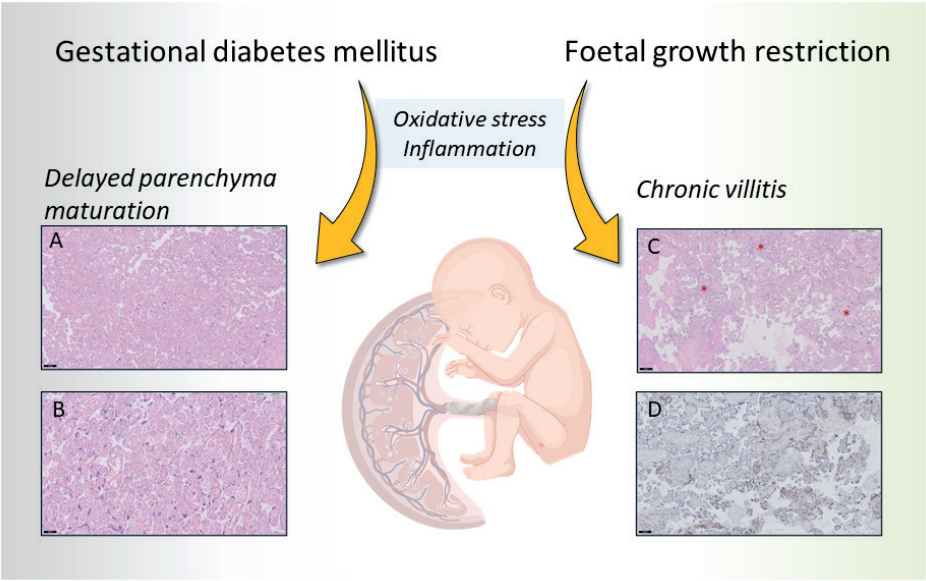

Figure 3. Histology of placental lesions in gestational diabetes mellitus and fetal growth restriction. Representative light microscope photographs of Hematoxylin/Eosin-stained placental samples. The excessive oxidative stress and inflammation in gestational diabetes mellitus and fetal growth restriction result in structural abnormalities in the placental vasculature leading to altered perfusion and fetal growth. Gestational diabetes mellitus is accompanied by delayed maturation of the parenchyma where there is an increase in villous capillaries (A, B). Placentas from pregnancies with fetal growth restriction show with chronic villitis (E-F) presenting lymphocytic infiltration (*) in the villi (C). Infiltration of T-cells is identified by positive CD3 staining (D).

The maternal immune response adapts to accommodate the fetus in multifactorial ways, and an aberration in any aspect can potentially lead to deterioration of fetal health. When such deterioration occurs, this could be interpreted as derailment of the *endo*-exposome. To prevent a harmful maternal immune response towards the fetus, some parts of the immune response are evaded, while other parts are directed to induce antigen-specific tolerance. [37] Both maternal- and fetal factors cooperate

to create an immunological 'fetus friendly' environment. The role and balance of different leukocyte lineages in gestational tissues are modified to secure a healthy pregnancy outcome. This includes restricting access and modifying the phenotypes of macrophages, dendritic cells, natural killer (NK) cells, and lymphocytes in various compartments of the uterus and placental membranes. [20,37,38] This restricted access is modulated by the production of several endogenous factors including immunoregulatory cytokines, chemokines, hormones and prostaglandins from both uterus and placental tissue.

Macrophages (especially the more anti-inflammatory subsets), dendritic cells, and regulatory T-cells (Treg-cells) that mediate immune tolerance also influence vascular dynamics through their potent anti-inflammatory capacity. Treg-cells are central players in maintaining immune tolerance. [39] These cells are powerful suppressors of CD4+ Th1/Th17 cells, inhibit generation of CD8+ cytotoxic T cells and NK cells, and interact with macrophages and dendritic cells for suppressing inflammation and maintaining immune quiescence. Uterine NK cells promote structural changes in the decidual vasculature for placental invasion and development. [40] The fetus, and its placental tissue in particular, contribute by bypassing or inactivating various maternal immune cells, through regulation of MHC antigen expression, excretion of complement regulatory proteins, and displaying other protective proteins. The fact that trophoblast has modified expression of classical HLA class I (with absence of HLA-A and HLA-B, and attenuated HLA-C) is considered one of the key protective mechanisms from the fetal side. These classical HLA antigens are polymorphic, and the paternally inherited antigens are therefore recognized as foreign. Nonclassical Ib antigens (HLA-E, HLA-F, HLA-G) are expressed instead. These Ib antigens are relative non-polymorphic and are not recognized as foreign by the maternal immune system. [36]

For GDM it is now becoming clear that inflammatory processes play a significant role in the disease pathophysiology. Underlying mechanisms include a shift away from a pro-tolerance immune environment due to diminishment of protective mechanisms or dominating exogenous or endogenous pro-inflammatory agents. For example, deficient signaling to A_{2B} adenosine receptors activation results in a lower capacity to reduce the generation of $O_2^{\bullet-}$ and $ONOO^-$, thereby increasing oxidative stress. This phenomenon also leads to insufficient protection against inflammation due to reduced generation of the anti-inflammatory cytokines IL-10 and adiponectin, but increased generation of the pro-inflammatory cytokines TNF and IL-6 in GDM and gestational diabetes. [41,42] In preeclampsia, failure of trophoblast cells to invade and remodel the maternal spiral arteries results in exaggeration of a systemic inflammatory process. Immunocompetent cells are activated and hypoxic conditions, excessive inflammation and/or oxidative stress occurs resulting in increased trophoblast failure. [43]

DIETARY INTERVENTIONS TO PREVENT PREGNANCY COMPLICATIONS

Therapeutic approaches to modulate excessive oxidative stress and the associated adverse inflammatory reactions in pregnancy complications could benefit pregnant women and their fetuses. However, due to potential teratogenic effects, pharmaceutical interventions during pregnancy are scarcely studied and thus have limited approvals for community use. Recently, prevention of pregnancy disorders through dietary intake has received more attention as a tractable and potentially effective intervention.

Nutritional interventions in patients with different forms of pregnancy complication and different outcome measures have been examined. One of these investigations is the Dietary Approaches to Stop Hypertension (DASH). [44,45] This diet was originally designed to normalize blood pressure in patients with hypertension. The DASH dietary pattern is low in fat, with a focus on reduced saturated fats compared with a high-fat diet. The rationale for the study was that the DASH diet would be expected to have a beneficial effect on pregnancy outcomes and reduces macrosomia in fetuses of mothers with GDM. Unfortunately, analyses of the data are hampered by the many differences between these two diets besides the fat content.

Furthermore, it is reported that dietary intervention in women at high risk for GDM may reduce inflammation and the risk of GDM. A reduction and improvement in carbohydrate quality rather than a restriction in the high-fat content in the diet plays a major role. The habitual diet plays an important role in the improvement that can be expected from dietary adaptation as seen in women with GDM. [9,46] Therefore, dietary intake has been considered as a potential treatment option (Figure 4). Below we summarize data of the most promising nutritional interventions, especially in relation to GOS.

L-arginine

The cationic amino acid L-arginine is considered as the biological precursor for ·NO, a potent endothelium derived vasodilator. [47] Increased synthesis of ·NO is associated with normal vascular adaptation under physiological conditions, while decreased ·NO synthesis has been reported in preeclampsia. [48] It is proposed that uptake of L-arginine is a phenomenon linked to generation of ·NO via the endothelial NO synthase (eNOS) in the fetoplacental endothelium. [49] This phenomenon seems to be restricted to the human cationic amino acid transporters 1 (hCAT-1) since the Michaelis-Menten constant (Km) for its activity was in the range of this plasma membrane transporter isoform, i.e., apparent Km 50-350 mmol/L. [50] Also, the potential link between L-arginine transport and ·NO synthesis may involve a very

high-affinity transport mechanism (Km ~2 mmol/L) describing system y+L activity. [49,50] Thus, the availability of L-arginine for its uptake via hCAT1 and system y+L into nearby eNOS localized in the vascular endothelium may be critical for the vascular adaptive regulatory mechanisms opposing vasoconstriction in preeclampsia. [51]

During pregnancy, an L-arginine rich diet as a source of substrate for the •NO synthesis and consequent vasodilation shows promise in protecting against preeclampsia. Although L-arginine results in vasodilation through •NO, the influence of L-arginine administration on blood pressure is disputed and the mechanism underlying its antihypertensive action is unclear. While studies of high doses for short periods have not demonstrated effects on blood pressure, prolonged low doses dietary supplementation of L-arginine (3 g/day) for 3 weeks has shown to decrease blood pressure through increased synthesis and bioavailability of •NO in women with preeclampsia. [48] Although a recent meta-analysis suggests that intervention with L-arginine may reduce FGR and result in increased birth weight, no reduction in the occurrence of preeclampsia in human pregnancies could be confirmed. [52] Another study showed however that in high-risk pregnancies, daily intake of medical food bars containing L-arginine plus antioxidant vitamins significantly reduced the incidence of preeclampsia compared to placebo. [51] The protective effects may be greatest when onset of the supplement is before 24 weeks of gestation. [51,52]

In early-onset preeclampsia, the human placental microvascular endothelial cells (hPMECs) show reduced capacity of •NO synthesis compared with hPMECs from late-onset preeclampsia. [53] The proposed mechanism behind these differences in the capacity of NO synthesis in hPMECs involves an elevated extracellular adenosine concentration as reported in human umbilical blood in preeclamptic pregnancies. Adenosine activates A2A/A2B adenosine receptors that induce the expression of VEGF which, via activation of VEGFR1/2, increases the activity if the inducible NOS form (iNOS) expressed in hPMECs. In early-onset, and in a minor degree in late-onset preeclampsia, the released VEGF in response to adenosine binds to sFlt-1 restricting VEGF biological actions. It is worth noting that L-arginine is taken up by the endothelium via plasma membrane mechanisms with a maximal transport capacity –defined as the ratio between the maximal velocity of transport over the affinity of membrane transporters for this amino acid [50]- could be rate-limiting for the •NO synthesis via eNOS. [54] The transport activity via hCAT-1 isoform and hCAT-2B, a splice variant of hCAT-2A isoform, is the main mechanism leading to uptake of L-arginine (apparent Km 50-350 mmol/L) and is concentrative leading to ~10-fold intracellular accumulation of L-arginine compared with its plasma concentration (~100 mmol/L). Since the affinity of eNOS for L-arginine is ~2-3 mmol/L, it may be a limiting mechanism for the synthesis of NO in preeclampsia. Therefore, supplementing women with preeclampsia with this amino acid may not necessarily restore the reduced •NO synthesis by the feto-placental endothelium.

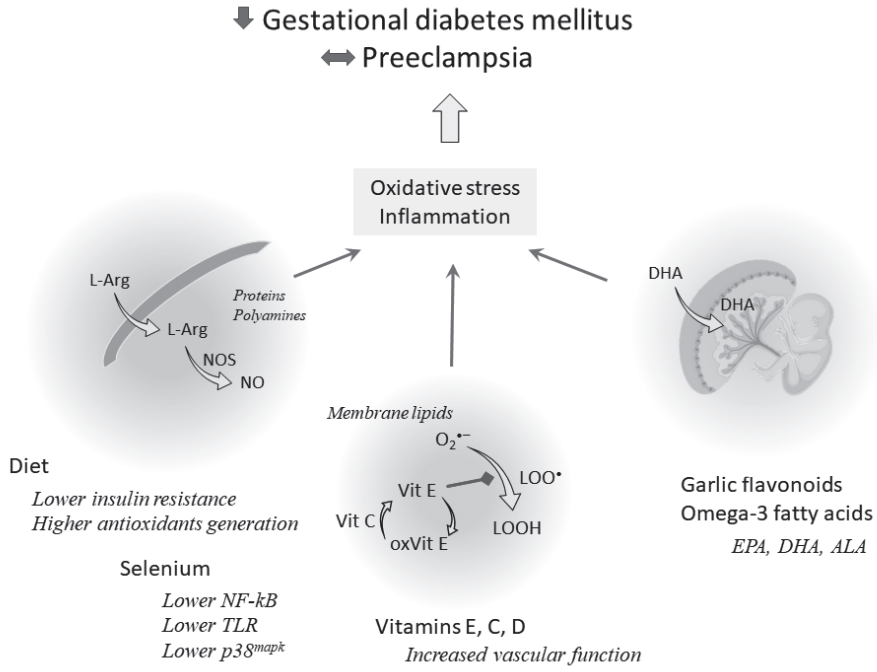

Figure 4. Dietary and other interventions to prevent pregnancy complications. Among the several intervention strategies implemented to avoid pregnancy complications, diet and supplementation with micronutrients are described. Diet interventions with a selection of healthy foods result in reducing insulin resistance and increasing the antioxidant capacity in pregnant women. Supplementation with essential trace elements such as Selenium reduced the level of prooxidant molecules. A generalized mechanism to improve placental function after diet or Selenium is a higher generation of nitric oxide (NO) by NO synthase (NOS) favored by higher uptake of its substrate L-arginine (L-Arg). This pathway seems favored compared with the use of L-Arg to the synthesis of polyamines and proteins. Supplementation of patients with the micronutrients vitamins E (Vit E), C (Vit C), and D (Vit D) diminishes the formation of lipid hydroperoxides (LOOH) from peroxy radicals (LOO•) when the anion superoxide ($O_2^{\bullet-}$) levels are higher in membrane lipids. This phenomenon results from the action of Vit E reducing (red line) the formation of LOOH, causing oxidation of Vit E (oxVit E). Vit E is restored from oxVit E involving Vit C. These mechanisms result in a lower membrane lipids oxidation. Vit E, Vit C and Vit D function restore endothelial dysfunction in the vasculature and other tissues. Garlic flavonoids and Omega-3 fatty acids also restored placental function involving the mother-*to*-fetus transplacental transfer of icosapentaenoic acid (*EPA*), docosahexaenoic acid (*DHA*), and alpha-linolenic acid (*ALA*). DHA is reported to accumulate in the placenta in diseases showing reduced or deficient membrane transport activity for this type of Omega-3. A healthy diet, physiological levels of Selenium, vitamins and Omega-3 fatty acids result in reducing oxidative stress and inflammation in pregnancy. This phenomenon reduces (ò) the risk of developing gestational diabetes mellitus with a less more evident effect (ó) in preeclampsia.

Fatty acids

Omega-3 (N-3) fatty acids possess antioxidant and anti-inflammatory properties and play a role in promoting placental vasculature. [55] The precise effect on lowering oxidative stress depends on the dosage, background diet and experimental conditions. [56] The three types of omega-3s include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). The long chain EPA and DHA are found in fatty fish, while ALA is found in oils from plant origin, such as flaxseed oil and chia seed. Interestingly, DHA supplementation in women with GDM, despite their pre-pregnancy BMI, resulted in an increased DHA level in the mother but not in the fetal circulation. [57] This observation has been partially explained by a reduced placental transport of DHA likely through the major facilitator super family domain containing 2a (Mfsd2a) transporter [58] resembling mechanisms operating in the blood-brain barrier. [59] The reported accumulation in the placenta in GDM pregnancies may reflect reduced transport to the fetus [60], since offspring born after GDM pregnancies have been reported to have lower DHA status at birth.

Thus, maternal supplementation with DHA in pregnancy may be useful to counteract GDM-associated oxidative stress and inflammatory response, while having minor or no direct effect on the fetus, and a likely positive indirect effect.

Omega-3 fatty acids might act better in combination with vitamin E because of its sensitivity to oxidation and strong synergistic activity on related markers. In a co-administration trial in women with GDM, administration of 1000 mg n-3 fatty acids from flaxseed oil plus 400 IU vitamin E per day resulted in improved oxidative stress biomarkers (TAC, NO, and MDA). [61] There was no improvement of the inflammation biomarker 'high- sensitive C-reactive-protein' and other pregnancy outcomes. [61]

The short chain fatty acid alpha-linolenic acid (ALA) is known as a universal oxidant because of its hydrophobic and hydrophilic characteristics. Administration of ALA improved markers of glucose metabolism and some markers of liver function, and increased adiponectin (A), A/L ratio and A/H ratio and decrease of L/A values. [62,63] Thus, although omega-3 fatty acids and especially ALAs seem to have beneficial effects on metabolic profiles, biomarkers of oxidative stress, inflammation, the effects on adverse pregnancy outcomes are less imminent. This phenomenon may in part be explained by the fact that an increase in the n6 linoleic acid will impact the production of LCPUFAs, e.g., suppressed DHA and EPA production favoring a higher ARA status. Interestingly, the modern Western diet contains an imbalance in the omega-6/-3 ratio due to lower omega-3 intake and higher omega-6 consumption. [64]

Vitamin B12, C, D and E

Vitamins and minerals have a substantial positive influence on the health of women and their fetuses. Adequate maternal micronutrient status is critical during pregnancy, and an inadequate micronutrient status associates with several pregnancy complications. [65,66] Antioxidant vitamin supplementation is considered a therapeutic or even preventive option for reducing inflammation and oxidative stress in placenta pathology.

Vitamin B_{12} (cobalamins), member of the vitamin B complex, is a cofactor for several enzymes involved in carbohydrates, fatty acids and amino acids metabolism, maintaining fetal growth and maternal metabolic state. In addition to these functions, vitamin B_{12} is also a scavenger of ROS, particularly $O_2^{\bullet-}$ and vitamin B_{12} deficiency increases the risk of GDM. [67–70] Patients with GDM are increasingly treated with the oral hypoglycemic drug metformin. Since metformin restricts the absorption of vitamin B_{12} [71], metformin-treated women with GDM may present lower levels of vitamin B_{12}. [72] However, metformin does not alter the active form of vitamin B_{12}, holotranscobalamin, suggesting that a reduced absorption of vitamin B_{12} may not alter the level of its active form. Interestingly, no effects of vitamin B_{12} on the development of the classical GOS have been reported in the literature.

Vitamin C and E are often supplemented in combination because *in vivo* and *in vitro* studies have shown that vitamin C and E act in synergy. Vitamin E is considered crucial in interrupting the cycle of lipid peroxidation, while vitamin C enhances the capacity of vitamin E to preclude lipid peroxidation by renewing oxidized vitamin E to its reduced form. Women at low risk of preeclampsia show no further risk reduction after supplementation of vitamin C solely [73], or after vitamin C plus E supplementation. [74,75] A trend of lower incidence of pregnancy induced hypertension was shown after 100 mg tocotrienol-rich-fraction of palm oil vitamin E per day. [76] However, in women with essential hypertension, there was no reduction in risk of superimposed preeclampsia or aggravation of hypertension after supplementation. [77] These findings were similar to previous reports showing that supplementation did not reduce the incidence of preeclampsia, irrespectively of risk at enrolment or early onset. [78] In a group of pregnant women with type 1 diabetes mellitus, i.e. at high risk for developing preeclampsia, the DABIT trial also failed to demonstrate reduction of the risk of preeclampsia and gestational hypertension after supplementation with vitamin E combined with vitamin C. [79] Similarly, another study assessed among high- and low-risk women whether vitamin C plus E supplementation reduces the risk of developing gestational hypertension. [80] This study concluded that supplementation did not reduce the risk of preeclampsia, and unexpectedly found that supplementation with vitamins C and E increased the risk of fetal loss or perinatal death.

The lack of beneficial effects of vitamins C and E supplementation in some studies could be explained by the fact that these women may have had an adequate antioxidant status at study initiation. There is some evidence that in women with low antioxidant status, such as in developing countries and low socioeconomic status, early administration of enriched milk containing several minerals and vitamins starting in first trimester, including 200 mg vitamin C and 400 mg vitamin E, reduced the incidence of preeclampsia. [81] The effect on birthweight is even more diverse, with some studies finding lower birth weights in the groups receiving antioxidants or high dose vitamin E. [78,82] Furthermore, it might also well be that too high concentrations of antioxidants may affect the normal physiology of reactive species.

Regarding preterm birth, there are conflicting reports of the effects of vitamin C and E supplementation. As ascorbic acid is one of several factors associated with preterm premature membrane rupture (PPROM, <37 weeks of gestation), it is thought to have a potential preventive effect. Vitamin C is involved in collagen synthesis and may maintain the integrity of the chorioamniotic membranes. In fact, reduced vitamin C levels are associated with spontaneous preterm birth. Contradictory results of supplementation are found regarding the risk of premature rupture of membranes (PROM). Supplementation of 100 mg vitamin C per day has been shown to reduce the incidence of PROM in healthy pregnant women. [83] Whereas other trials found higher rates of PROM and PPROM. [80,84]

Besides vitamin C and E and their combination, vitamin D has also been studied extensively in pregnant women. Vitamin D is shown to have an immunomodulatory effect, and may play a role in maintaining immune tolerance in pregnancy. [85] Studies on the effects of supplementation with vitamin D on GOS show inconsistent findings. [86,87] Some studies report no influence of administration of vitamin D on the prevalence of preeclampsia [88,89], whilst others describe a positive effect on the prevalence of preeclampsia. [90,91] There are contradictory reports on the effect of birth weight and the prevalence of preterm labor. [88,90–92] Both Fogacci et al. [91] and Ali et al. [90] found a decrease in the prevalence of FGR. It is reported that supplementation with vitamin D in 2,487 women reduced the risk of preeclampsia, FGR and preterm birth and was dependent on the doses of vitamin D but independent of supplementing with vitamin D alone or together with calcium. [91] Although these findings are difficult to reconcile, it remains possible that a beneficial effect of vitamin D supplementation to prevent or alleviate the signs and symptoms of preeclampsia may apply in certain high risk populations. [88,90,91]

More extensively the effects of vitamin D on women with GDM have been described. Women with GDM showed low vitamin D levels compared with the level of this micronutrient in normal pregnancies (>20 ng/L, measured as serum 25hydroxyvitamin D, 25(OH)D). [93–97] Vitamin D supplementation varied between

200–1,000 IU/day (5–25 mg/day) to reduce the risk of developing GDM. Vitamin D in combination with calcium or in combination with omega-3 fatty acids improves the glucose and lipid metabolism of patients with GDM. [97,98] However, supplementation of vitamin D is an approach that has been not conclusive in women with GDM. [88,90,95] A unique intramuscular administration of a high dose of vitamin D (300,000 IU) has been shown to improve the status of its metabolic product 25(OH) D3 in women with GDM. [99] Recently, co-administration of vitamin D in combination with zinc, magnesium and calcium in women with GDM showed a significant reduction in serum high-sensitivity C-reactive protein and plasma malondialdehyde concentrations, as well as a significant increase in total antioxidant capacity levels compared to placebo. [100]

Even when vitamin D levels are improved, there is a question of how this approach relates to the duration of the beneficial effect in these patients and their fetuses and newborns. The biological actions of vitamin D include activation of vitamin D receptors in the fetoplacental endothelium [101–103] protecting against oxidative stress and endothelial dysfunctional metabolism, including a reduced mitochondrial oxidative phosphorylation. [102] Thus, lower level of vitamin D and altered activation of vitamin D receptor in GDM may increase $O_2^{\cdot-}$ which scavenges NO limiting most biological actions of this gasotransmitter [104]. HUVECs from GDM show increased eNOS activity, thus, a reduced eNOS activation due to deficient vitamin D activation of vitamin D receptors and the increased NO scavenging by $O_2^{\cdot-}$ may not be enough to limit the NO-mediated inhibition of cytochrome *c* oxidase seen in GDM. [105]

Selenium

Similar to vitamins, minerals with antioxidant function are also associated with pregnancy outcomes and have been used in several trials. A good example of this is selenium. Selenium (Se) is an essential trace element that functions via incorporation in protein forming selenoproteins. These proteins have both antioxidant and anti-inflammatory effects. Se possesses anti-inflammatory activity due to its regulatory effect on expression of pro-inflammatory genes, including *selenoprotein S* gene and the release of pro-inflammatory cytokines.

Selenium is mostly obtained from dietary intake of nuts, cereals, meat, mushrooms, fish, and eggs. The dose of intake remains subject of discussion; one study recommends dosage of 10 up to 56 mg/day while others recommend the intake of 25-50 mg/day, irrespective of diet. The recommended allowance is 55 mg Se/day for healthy adult non-pregnant women; however, it is likely that substantially higher levels are required during pregnancy. Higher blood level of Se associates with improved markers of oxidative stress, inflammation, insulin metabolism and obstetrical outcomes. The concentration of Se varies in a wide range in both pregnant

women and non-pregnant women, due to variable global distribution and ubiquitous dietary sources. The blood concentration of Se reflects the daily intake and higher blood concentration of D-glucose correlates with lower Se blood levels in pregnant women with GDM [106], a phenomenon likely due to the potential state of insulin resistance in these women.

Supplementation with Se decreases oxidative stress and alleviates inflammation in pregnant women. Selenium reduces inflammation by inhibiting NF-κB, toll-like receptors and 38 kDa mitogen-activated protein kinases ($p38^{mapk}$) pathways in several cell types including HUVECs. [107] Oxidative stress is also reversed by Se due to its capacity to activate D-glucose uptake and metabolism thus reducing the state of hyperglycemia seen in patients with GDM. [108] In a trial performed in Iranian women from Arak [109–111], administration of Se did not change the maternal HOMA β-cell function, lipid profile, plasma NO level, or total antioxidant capacity. Although Se supplementation resulted in beneficial effects on glucose metabolism and oxidative stress and inflammation markers in pregnant women, it did not reduce the incidence of PE, and no similar results were described for FGR and preterm birth. These results should be considered with caution however, since they refer to a small sample size and women from the Arak region have higher selenium concentrations than women from other regions of Iran.

Serum levels of least 100 mg Se/L are needed for maintaining adequate Se mediated antioxidant capacity. Because both plasma levels below 45 mg/L and decreased GPx activity are associated with advanced pregnancy outcomes, supplementation should be considered for those having suboptimal blood Se levels. However, the underlying mechanism of the role of Se and the Se-dependent enzymes stays unclear. Moreover, the dosage, timing and duration of Se supplementation during pregnancy is still subject of debate.

Iron

Pregnant women are at risk of developing iron deficiency anemia. Therefore, the World Health Organization (WHO) recommends iron supplementation early in pregnancy. [112] Anemic pregnant women have a higher incidence of preterm birth and offspring with low birth weight. [113] Korkmaz et al. [114] found in a randomized double-blind controlled trial that iron supplementation during first trimester is associated with higher levels of oxidative stress. No correlation with preeclampsia was found. [114] On the other hand, Siddiqui et al. [115] found an increased risk of developing preeclampsia in women with pre-existent high serum iron levels. [115] Also, in a study in which iron supplementation before 16 weeks gestational age was started, an increased risk of developing hypertension after 20 weeks gestational age was apparent. [116] Iron influences the production of ROS in the placenta contributing

to oxidative stress [113] via the formation of hydroxide (OH^-) and hydroxyl radical ($^•HO$). [11] It is interesting that both a low hemoglobin (Hb) status as well as a high Hb status is associated with pregnancy complications. [113,117,118] Increase in iron (both pre-existent plasma ferritin levels and supplementary iron) is also associated with a higher risk of developing GDM. [11,119,120] So, although iron supplementation could be beneficial in anemic pregnant women, iron levels need to be monitored to prevent overload and secondary complications like GDM.

Discussion and Conclusion

Oxidative stress and inflammation are involved in the pathophysiology of various pregnancy complications collectively described as "the Great Obstetrical Syndromes". Nutrient and dietary interventions can play a role in favorably attenuating the processes of oxidative stress and inflammation by configuring a more protective exposome. It is known that unhealthy diets characterized by energy dense but not nutrient dense foods result in more unfavorable outcomes attributable to inflammation and oxidative stress. However, the beneficial effects of various dietary interventions on pregnancy outcomes through modulation of inflammatory processes and oxidative stress are still controversial. Research on this topic is challenging for several reasons:

(1) A causative relation between adverse outcomes, dietary intake, oxidative stress and inflammation is hard to prove, largely because of the complex heterogeneity of many risk factors that include not only *ecto*-exposome and *endo*-exposome, but also inter-related and independent factors like BMI and smoking, as well as socio-economic status and ethnicity.

(2) The onset of supplementation during pregnancy might simply be too late to have a beneficial effect. Most of the tested interventions are initiated in the second trimester of pregnancy while most likely the underlying causal events giving rise to placental dysfunction occur prior to that time. Therefore, introduction of antioxidant or vitamin supplementation before or around conception might be more effective, since a woman's health and nutrition status before pregnancy is crucial for improving pregnancy health. [121]

(3) The interventions have been conducted in a wide variety of study populations (baseline characteristics), mostly in studies with a small number of participants and different outcome measurements. There were differences in nutritional state, race, social economic status, background, food patterns, culture, start, duration, dosage and route of administration of the interventions. Due to differences in study design and objectives, the outcomes cannot be compared directly.

(4) The susceptibility of the developing fetus is an important consideration, so once potential interventions are identified they must be evaluated for their safety and any effects on the development of the embryo and fetus.
(5) Dietary intake exists of many constituents that interact together. It is not to be expected that changing one single component for a limited period of time will lead to immediately measurable effect.
(6) Systematic report bias can occur through non-objective self-reported food questionnaires and interventions can be confounded by this bias.

In other diseases, for example inflammatory bowel disease (IBD), preventive dietary interventions are thought to be useful. [122] Some of the underlying oxidative stress and immunological inflammatory mechanisms are comparable between IBD and pregnancy complications. Therefore, the proven effective treatment of diet in IBD might be translated to candidate dietary treatments for pregnancy complications. [122] In contrast, the desired effect in IBD patients (less disease activity) is different to that in pregnancy (less FGR and hypertension), which could influence patient motivation. In the future, diets with focus on changes in multiple nutritional aspects could be developed as a candidate intervention, considering the potency as well as the complexity of nutrition. Since a balanced diet consisting of healthy foods is by definition not harmful, it might be beneficial if it also solves nutritional deficiencies. Because pharmacotherapeutic treatment is restricted in pregnancy, pregnant woman reasonably would be expected to benefit from healthy nutritional approaches, regardless of impact on GOS outcomes.

A limitation of the current review is that a considerable proportion of the included studies were published by only a limited number of research groups. Most trials were of small sample size, short duration and often local dietary recommendations and/or supplementation guidelines were not known, nor patient compliance reported. Most randomized controlled trials of supplementation during pregnancy to reduce pregnancy complications reported controversial or negative results, despite the expected protective associations between dietary antioxidant and pregnancy outcomes demonstrated in observational studies.

In summary, the multiple exogenous and endogenous factors involved in placental and fetal development and growth are crucial elements of the exposome to which the mother and fetus are exposed. [7,123] Dietary interventions envisage reaching levels of the modulatory factors involved in suppressing oxidative stress to a physiological level, in order to promote positive pregnancy outcomes in women at high risk for pregnancy complications. In this phenomenon, the activation of the

endo-exposome as consequence of dietary interventions might be essential to explain the inflammation and redox regulatory mechanisms involved in achieving a healthy pregnancy. Evaluation of dietary interventions will need to account for the many other factors that predispose to GOS. For example, increased maternal age is associated with increased pregnancy complications like preeclampsia and GDM [124], and an interaction between age and nutritional effects may exist.

In conclusion, nutrition is considered key to maternal optimal health before and during pregnancy to optimize birth outcomes. Inflammation and oxidative stress have been implicated in the most common pregnancy complications like GOS, and interest in diet as a possible positive factor has grown. Now is the time for further assessment of anti-inflammatory and fully-fledged nutrition in pregnancy with attention on the timing, duration and contents of the dietary intervention, with the benefit of a reduced risk of potential adverse effects compared to pharmacotherapeutic interventions.

Conflict of interest

The authors declare no competing interests.

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