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Review

Oxidative Stress in Early Life and Later Obesity Development

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ABSTRACT

Critical time windows exert profound influences on foetal physiological and metabolic profiles, which predispose an individual to later diseases via a 'programming' effect. Obesity has been suggested to be 'programmed' during early life. Foetuses and infants who experience adverse growth are subjected to a higher risk of obesity. However, the key factors that link adverse foetal growth and obesity risk remain obscure. To date, there is considerable evidence showing that the overall balance between free radical damage and the antioxidative process being challenged occurs throughout gestation. With the view that pregnancy is a pro-inflammatory state confronted with enhanced oxidative stress, which possesses similar characteristics to obesity (a chronic inflammatory state with increased oxidative stress), oxidative stress is thus biologically plausibly be proposed as the underlying mechanism between this causal-disease relationship. Oxidative stress could act as a programming cue for the development of obesity by inducing complex functional and metabolic deregulations as well as inducing the alteration of the adipogenesis process. Thereby, oxidative stress promotes adipose tissue deposition from early life onwards. The enhancement of fat accumulation further exaggerates oxidative derangement and perpetuates the cycle of adiposity. This review focuses on the oxidative stress pathways in prenatal and early postnatal stages, from the aspects of various endogenous and exogenous oxidative insults. Because oxidative stress is a modifiable pathway, this modifiability suggests a potential therapeutic target to fight the obesity epidemic by understanding the causal factors of oxidant induction.

Key words: Antioxidants, foetal growth, obesity, oxidative stress, pregnancy

INTRODUCTION

Obesity is a chronic disorder which is defined as excessive body fat deposition that presents an adverse effect on health (Fernandez-Sanchez *et al.*, 2011). Obesity is multifactorial in origin. Fundamentally, obesity is caused by excessive energy intake compared with energy expenditure (Sikaris, 2004). One of the theories that explain the cause of obesity is 'foetal origins of adult disease' hypothesis, suggesting that *in utero*

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environment is capable of modulating the physiologic and metabolic functions of the foetus, resulting in disease 'programming' (Barker, 2004).

A dramatic rise in overweight and obesity are observed worldwide. Globally, more than 10% of the world's adult population are obese (WHO, 2013). The Third National Health and Morbidity Survey (NHMS III) conducted in 2006 revealed the prevalence of overweight in Malaysia to have increased from 16.6% to 29.1% (IPH, 2008), while obesity prevalence tripled from 4.4% to 14.0% in comparison to statistics from NHMS II in 1996 (Fatimah *et al.*, 1997). The updated NHMS in 2011 reported that the prevalence of overweight and obesity were 29.4% and 15.1% respectively, with a noticeable higher percentage of obesity for women at 17.6%, compared to men at 12.7% (IPH, 2011).

The prevalence of overweight and obesity are also increasing in children (WHO, 2013). Worldwide, the prevalence of overweight and obese children under the age of 5 in 2010 was 6.7% and was expected to reach 7.8% in 2015 (de Onis, Blössner & Borghi, 2010). The latest national prevalence of overweight and obesity for children under 5 years old was 6.1%, with a higher proportion among boys (7.6%) than girls (4.6%) (IPH, 2011). By age group, the highest prevalence was noted among children aged 5 to 9 years (IPH, 2011). This rising problem of obesity has led to the development of prevention and intervention programmes against the disease starting in early life. Thus, understanding the underlying causes is crucial to combating the onset of the pathology.

THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE HYPOTHESIS

The concept of early life experience on later health outcomes is not new. This causal-disease relationship has come to light in recent decades and forms the basis of the 'foetal origins of adult disease' hypothesis, which was proposed by Dr. Barker in the early 1990s. He proposed that the intrauterine environment has the capacity to modulate the physiological function of the foetus, resulting in disease 'programming' (Barker, 2004). It is suggested that physiologic, metabolic and structural adaptations (programming) are made by foetuses when exposed to adverse (malnutrition) early environments, to increase the chance of survival. However, early programming conflicts occur when postnatal conditions are improved, such as in a food-abundant environment (Cottrell & Ozanne, 2008). In the long term, these programming changes are subsequently translated into pathology, leading to an escalated risk of chronic diseases.

Today, the early life origins hypothesis is now described as the 'developmental origins of health and disease (DOHaD) hypothesis', to explain the association between foetal and infant growth patterns with later disease development (Langley-Evans, 2006). Either smaller or larger birth size is associated with an increased risk of disease. Several mechanisms have been proposed to elucidate the underlying factors of foetal growth variations (Cottrell & Ozanne, 2008; Taylor & Poston, 2007). Recently, oxidative stress has been shown to act as the effect modifier for this causal-disease association. Therefore, this review focuses on the oxidative stress pathways, which explain the linking factor underlying 'programming' association between foetal growth and subsequent obesity risk. Given the modifiable nature of the oxidative stress level, a multitude of factors that influence the alterations of the oxidative status during prenatal and early postnatal stages are discussed.

Disruption of the oxidative status in pregnancy

Oxidative stress arises when an excessive generation of reactive oxygen species (ROS)

is not counterbalanced by intrinsic antioxidant defence mechanisms (redox status imbalance) (Lázár, 2012). Pregnancy is a pro-inflammatory state that is exaggerated with a variety of pro-oxidants from both endogenous (e.g., enzymatic and mitochondrial respiration) and exogenous (e.g., diet and pollutant) origins (Furness, Dekker & Roberts, 2011). Changes in metabolic and physiologic profiles throughout gestation predispose a pregnant woman to systemic oxidative stress (Ghate *et al.*, 2011; Saikumar, Jaya & Renuka Devi, 2013).

During pregnancy, ROS is required to contribute to embryonic development and placental remodelling through signal transduction (Lázár, 2012). The increased mitochondrial oxidative metabolism from reduced uteroplacental perfusion as well as the increased energy demand and oxygen requirement of the mother and foetus exaggerates free radical formation (Quanungo & Mukherjea, 2000; Zavalza-Gomez, 2011). The inability to increase oxidative stress and to generate redox-related signalling could lead to deregulation of the development process (Dennery, 2007). In this case, higher oxidant levels are expected in pregnant women than in non-pregnant women as evidenced by other studies (Bukhari *et al.*, 2011; Stefanoviæ *et al.*, 2012). Under normal conditions, the homeostatic concentration of ROS is maintained by enzymatic and non-enzymatic antioxidants (Burton & Jauniaux, 2011).

When a pregnant woman is exposed to environmental stimuli that are oxidant and pro-oxidant capable, or events occur in pregnancy such as maternal diabetes or hypertension, uncontrolled production of ROS and depleted antioxidant capacity attributed to the poor homeostatic adaptation of antioxidants defend the maintenance of the redox balance. These major perturbations could result in an oxidative attack that is capable of damaging biological molecules, such as lipids, proteins, polysaccharides and deoxyribonucleic acid (DNA) in maternal-foetal units (Chelchowska *et al.*, 2011), leading to poor foetal growth. This scenario is evidenced by a finding that indicated increased oxidative injuries and depleted antioxidant potential in newborns who were either small for their gestational age (SGA) or large for their gestational age (LGA), together with their mothers (Saker *et al.*, 2008).

Oxidative stress and obesity

In addition to the detectable oxidative stress in offspring who are born smaller or larger than average, studies have found changes of adipose tissue mass and insulin levels in these individuals. A U-shaped trend of birth size in relation to obesity has been s reported previously. Newborns with a small birth size who are prone to early catch-up growth in infancy and childhood have a higher tendency to store adipose tissue (Cottrell & Ozanne, 2008) and an increased insulin resistance (IR) (Chiavaroli *et al.*, 2009). On the other hand, newborns with a large birth size are inclined to increased adipose tissue deposition in infancy and childhood, which could relate to early adiposity rebound or reflect an inherited susceptibility to obesity (Chiavaroli *et al.*, 2009). The similarity of increased IR was observed in those children (Chiavaroli *et al.*, 2009).

Impaired insulin sensitivity is proposed to be induced by oxidative stress through pancreatic β-cell apoptosis at birth and weaning (Bruin *et al.*, 2008). Alternatively, the oxidants could impair insulin-signalling elements and reduce glucose transport activity in the myocytes (Henriksen, Diamond-Stanic & Marchionne, 2011), via modulation of gene expression (Campión *et al.*, 2006). Hyperinsulinemia as a result of pancreatic function deregulation as well as IR has been proposed to induce malformation in hypothalamic structures, causing body weight deregulation and obesity development (Cottrell & Ozanne,

2008). Therefore, such data could be regarded as evidence of underlying oxidant-induced metabolic alterations related to birth weight, which 'programme' the later development of obesity. Oxidative stress collectively plays a role as a programming cue in the development of obesity by inducing metabolic deregulation and adipogenesis alteration, which promotes adipose tissue deposition starting in early life. As demonstrated in Figure 1, the enhancement of fat accumulation further exaggerates oxidative derangement (Chiavaroli *et al.*, 2009) and the subsequent positive cycle of adiposity.

OXIDATIVE STRESS CAUSAL FACTORS

Prenatal and early postnatal environments exert potential oxidative stress effects on the growth and developmental process of the foetus and infant. These factors include

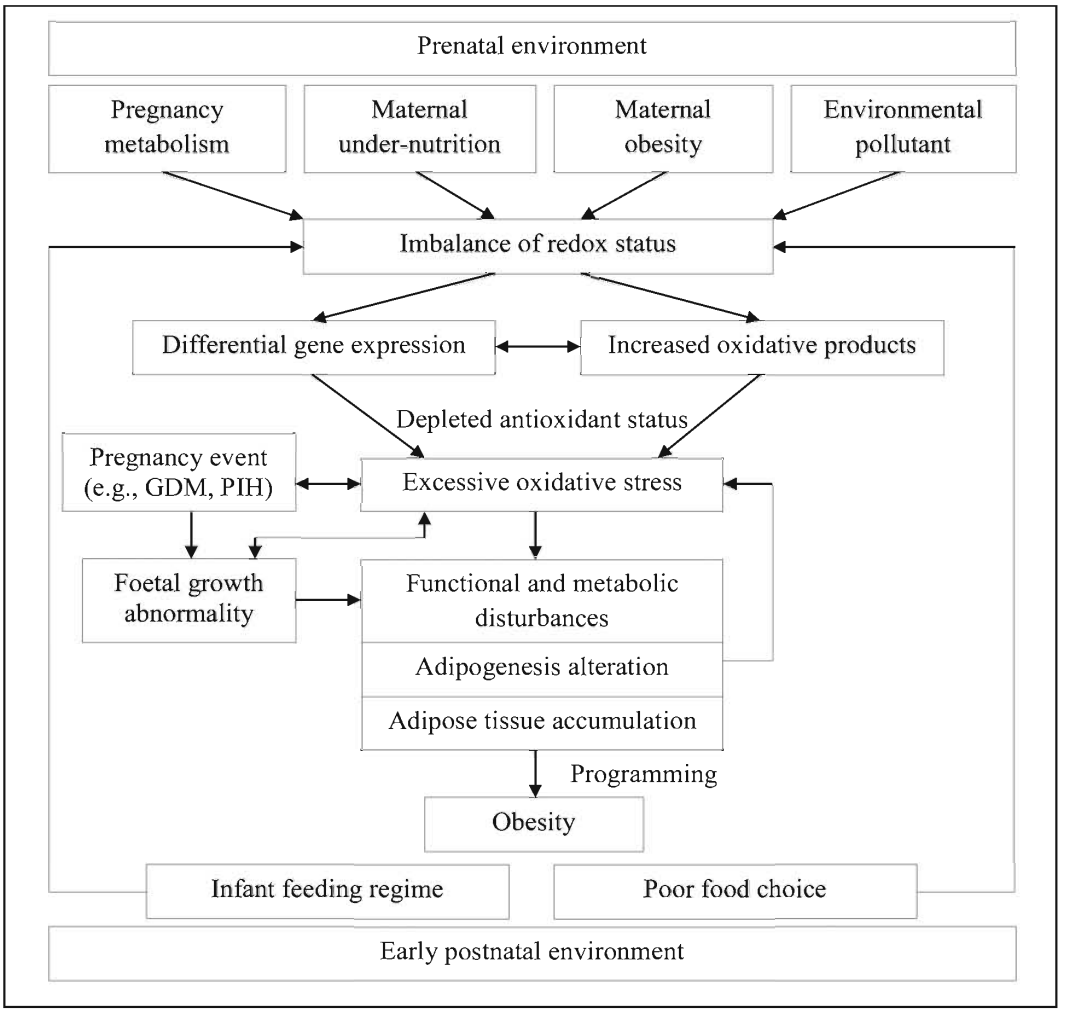

Figure 1. Factors in prenatal and early postnatal environments that provoke the surge of oxidative stress and induce the programming of obesity
Note. GDM=gestational diabetes mellitus; PIH=pregnancy induced hypertension

maternal nutrition, environmental pollutants, pregnancy events, the infant feeding regime and food choices in infancy and early childhood.

A. Prenatal environment

Maternal nutrition

The maternal nutrition environment which encompasses dietary intake, circulating nutrient, uteroplacental blood flow and nutrient transfer, is a dominant factor in determining foetal growth and consequent health (Stephenson & Symonds, 2002). Malnutrition (under-nutrition or over-nutrition) has been shown to impair energy balance systems and predispose to early onset of obesity (Cottrell & Ozanne, 2008).

Maternal undernutrition

Early findings on maternal nutritional deprivation with low birth weight and subsequent chronic diseases formed the basis of the 'thrifty phenotype hypothesis'. Maternal undernutrition refers to inadequate intake of various macronutrients and micronutrients. Protein deficiency could impair cellular antioxidant capacities because of its role as a synthesis component for the antioxidant defence system, such as glutathione and albumin (ROS scavenger) (Luo *et al.*, 2006). This assumption is confirmed by a previous study that showed that the extent of the depletion of the antioxidative enzyme activities and the enhancement of tissue lipid peroxidation were affected by the severity of protein deficiency (Huang & Fwu, 1993).

In comparison to energy or macronutrient malnutrition, the prevalence of micronutrient deficiency is higher because of a poor quality diet, especially in many nutrition transitional countries (Eckhardt, 2006). Plenty of micronutrients are anti-oxidants that interact or act synergistically to alleviate oxidant stress (Jacob, 1995). Inadequacy of metabolically related vitamins such as folate and cobalamin (B_{12}) promote hyper-homocysteinemia (Vigna *et al.*, 2011), which induces oxidative stress through auto-oxidation (Loscalzo, 1996), glutathione peroxidase (GPx) impairment (Upchurch *et al.*, 1997) or low density lipoprotein (LDL) oxidation (Pfanzagl *et al.*, 2003). Vitamin C deficiency reflects the loss of antioxidant protection that inactivates nitric oxide or increases cellular GPx concentrations, to counteract homocysteine-induced oxidative stress (Kanani *et al.*, 1999). Low dietary zinc has been associated with decreased superoxide dismutase (SOD) activity in overweight and obese individuals (Tungtrongchitr *et al.*, 2003), suggesting that a relationship exists between zinc deficiency, oxidative stress and obesity.

Changes in micronutrient status have been hypothesised to determine the changes of adiposity (García, Long & Rosado, 2009). In this context, an inadequate supply of maternal antioxidative nutrient could force the foetus to adapt to an enhanced *in utero* oxidative stress environment via gene expression and metabolic modulation, and subsequently programme the individual to acquire obesity. Supportive evidence is shown by the association between maternal dietary restriction in multiple vitamins and minerals with increased rat offspring adiposity, insulin resistance and oxidative stress as well as differential expression of adipokines (Lagishetty *et al.*, 2007; Venu *et al.*, 2004). In other words, micronutrient deficiency could increase fat deposition, which is regulated by antioxidant-mediated adiposity reduction.

The metabolic deficiency effects of micronutrients in influencing adipokines and lipid metabolisms have been reported in a review (García *et al.*, 2009). For example, Campión *et al.* (2006) found that dietary ascorbic acid reduced body weight and fat content in rats that were fed a high fat diet, through the down regulation of genes that are involved in adipogenesis, adipocyte differentiation, glucocorticoid metabolism and insulin resistance. In a separate study,

Aeberli *et al.* (2006) indicated that vitamin C, vitamin E and b-carotene intakes were significant negative predictors of leptin in overweight Swiss children. Development of insulin and leptin resistances resulting from altered gene expression caused by a deficiency in specific antioxidants, in turn, increases the risk of adiposity and obesity.

Maternal over-nutrition/ obesity

The association between maternal over-nutrition and adverse health outcomes is of particular concern recently because of the increasing rate of obesity. A similar development of an obese phenotype, which is comparable to a nutrition deprivation condition, is observed in the respective offspring. Maternal obesity is shown to further increase the susceptibility of a pregnant woman to oxidative injury, thus exacerbating the pathophysiological background of obesity development.

Obesity is a chronic inflammatory state that acts as a source of systemic oxidative stress (Piva *et al.*, 2013). Several mechanisms involving adipocyte-generating oxidative stress have been proposed. Excessive adipose tissue accumulation stimulates the rise of cytokines, which is attributed to the formation of free radicals (Fernández-Sánchez *et al.*, 2011). Adipose tissue is also responsible for the upregulation of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity via angiotensin II, which plays a significant role in the major route for ROS production in adipocytes (Fernández-Sánchez *et al.*, 2011; Furukawa *et al.*, 2004). Other mechanisms are through mitochondrial and peroxisomal oxidation of fatty acids, over-consumption of oxygen and lipid-rich or antioxidant-poor diet induction (Fernández-Sánchez *et al.*, 2011; Vincent, Innes & Vincent, 2007). Hence, the biomarkers of oxidative damage are higher in obese individuals and increase according to the magnitude of the adiposity and fat distribution (Amirkhizi *et al.*, 2010; Stefanoviæ *et al.*, 2012).

The authors speculate that the exaggeration of maternal oxidative stress induced by pregnancy obesity, in turn increases foetal oxidative stress and causes *in utero* adipokine deregulation and insulin resistance, which could predispose offspring to obesity. In support of this scenario, newborns with obese mothers were shown to be at high risk of developing the LGA phenotype, which is associated with oxidative stress (Chiavaroli *et al.*, 2009) and increased body mass index (BMI) in the future (Catalano & Ehrenberg, 2006). Malti-Boudilmi *et al.* (2010) noted that, even among AGA infants born to obese mothers, a higher oxidative stress was exhibited than their non-obese counterparts. Other evidence is based on the association between maternal obesity and infant body composition. The offspring from obese mothers were found to have higher levels of fat mass instead of lean mass (Catalano *et al.*, 2009; Catalano, 2010). Otherwise, a longitudinal cohort study reported that maternal pregravid obesity was the strongest predictor of neonatal adiposity and childhood obesity (Catalano *et al.*, 2009).

Environmental pollutants

Rapid global industrialisation has brought significant environmental changes and increasingly severe pollution. Prenatal exposure to airborne environmental chemical substances and tobacco smoke have been shown to increase oxidative stress and induce genotoxicity, causing long-term health effects (Mohorovic, 2004; Maritz & Mutemwa, 2012). There is evidence that maternal exposure to toxic agents from household sources, environmental tobacco smoke (ETS) or airborne particulate matter (PM), such as polycyclic aromatic hydrocarbons (PAH), nicotine and combustion-derived particles (CDP), are associated with an increased risk of intrauterine growth retardation (IUGR), preterm birth (PTB) and low birth weight (LBW) (Aycicek & Ipek, 2008; Delpisheh *et al.*, 2009; Wahabi *et al.*,

2013) which is especially critical in the earliest phase of embryo growth (Mohorovic, 2004). An *in vivo* study indicated that lower weight gain during lactation was found in offspring who had inhaled diesel exhaust particles (DEP) , which could be caused by transferring the toxicants via breast milk, thus delaying the biological effect from the point of exposure (Hougaard *et al.*, 2008).

Overall, this association could be explained by the detrimental oxidative stress programming effect that is induced by environmental toxicant exposure on birth outcome, either directly or indirectly. As proposed by Kannan *et al.* (2006) PM-induced oxidative stress could interrupt the transplacental oxygen and nutrient transport, or it could act through hemodynamic responses to restrict foetal growth. Mohorovic (2004) proposed that combustion-derived particles induced oxidative stress by directly inhibiting antioxidant and enzymatic activities, which subsequently adversely affected early embryonic development. Supportive evidence is reported by the higher level of oxidative stress in LBW infants who were born to smoking mothers (Aycicek & Ipek, 2008; Saker *et al.*, 2008; Tsui *et al.*, 2008). In an air polluted area, a higher degree of DNA damage was also observed in the maternal blood and placenta (Topinka *et al.*, 1997). However, the risk to exposure could be from individual differences, which depends on the presence of metabolic polymorphic genes (Delpisheh *et al.*, 2009).

Although born smaller in size, the environmental pollutant-exposed infants are associated with a higher risk of later obesity. This relationship is supported by the studies that found increased odds of paediatric overweight and obesity among children with mothers who smoked during pregnancy (Gorog *et al.*, 2011; Ino *et al.*, 2011). In one cohort study, prenatal pollution exposure (dioxin-like compounds PCBs and the pesticide metabolite DDE) was shown to be associated positively with BMI in children between 1 and 3 years of age (Mead, 2009). A possible mechanism is based on the rapid catch-up growth concept. Smaller infants are more susceptible to postnatal catch-up growth, causing greater adiposity in later life (Ong *et al.*, 2002). This relationship is supported by the common phenomenon of catch-up growth, which is normally observed post-natally in children with intrauterine smoke exposure. Women who smoke tend to prefer bottle feeding instead of breast feeding, leading to higher infancy weight gain (Fried, 2002). Altogether, these findings suggest that maternal exposure to environmental pollutants induce foetal and infancy growth variations, which could be mediated through pollutant-induced oxidative stress configurations followed by catch-up growth, thus increasing the risk of obesity.

Maternal diabetes

Gestational diabetes mellitus (GDM) is an altered redox state that acts as a significant source of foetal oxidative stress (Dennery, 2007). There is irrefutable evidence of oxidative stress in cases of diabetic mothers and their infants, including increased levels of xanthine oxidase, lipid peroxidation, lipoperoxide and proteolytic activity. The increased generation of ROS has been suggested to arise from the oxidation of glycated protein (Lázár, 2012) or the auto-oxidation of glucose and other small auto-oxidisable molecules, which are catalysed by transition metals (Hunt & Wolff, 1990). Alternatively, it could be attributed to the activation of xanthine oxidase (XO), the main free radical-producing enzyme, which results from hyperglycaemia, hormonal alteration or increased ATP breakdown (Biri *et al.*, 2006). Also, impairment of antioxidant defences could deactivate radical scavenger function. These proposed mechanisms establish explanations for the increased oxidant load that is seen in GDM mothers and infants.

The presence of oxidative stress was suggested to be implicated in the progression and/or pathology of GDM (Lo´pez-Tinoco *et al.*, 2011), resulting in biochemical and metabolic disturbances within the foetus and, thereby, programming foetal functional and developmental features. Rat embryos cultured under hyperglycaemic conditions showed significant growth retardation and development malformation, along with increased ROS formation and decreased glutathione concentration (Trocino *et al.*, 1995). In humans, microsomia or IUGRs could also be present in severe maternal diabetes that is complicated by vasculopathy and nephropathy, but with limited information on later consequences (van Assche, Holemans & Aerts, 2001).

On the other hand, a greater prevalence of macrosomic phenotypes was proven among offspring of diabetic mothers (Hillier *et al.*, 2007). Such foetal growth abnormalities resulting from GDM were associated with an increased rate of higher BMI and adiposity (Lindsay *et al.*, 2000; Vohr, McGarvey & Tucker, 1999), via the mediation of foetal insulin responses (van Assche *et al.*, 2001), which could be induced by oxidative stress (Bruin *et al.*, 2008). As reported by Hillier *et al.* (2007), the effect of hyperglycaemia in pregnancy on childhood obesity could also operate through normal birth weight offspring of diabetic mothers, which underlies the silent background effect of the oxidant load on metabolic programming, which is induced by excess glucose exposure.

Maternal hypertension

There is considerable evidence that oxidative stress acts as a key contributing factor to the pathogenesis of pregnancy-induced hypertension (PIH) (Lázár, 2012). Women with pre-eclampsia (PE) manifest abnormal ROS production and increased circulating markers of lipid peroxidation (Mistry *et al.*, 2008; Mohanty *et al.*, 2006), which are secondary to reduced placental perfusion (Roberts, 2000). Activation of the XO system (Bainbridge, Deng & Roberts, 2009) or stimulation of NADPH oxidase by AT1 receptor agonistic antibodies from PE women (Dechend *et al.*, 2003) was suggested to be a potential source of oxidative stress, increased ROS production and inflammatory responses. Otherwise, neutrophil activation in PE could produce excess ROS to trigger lipid peroxidation (Sharma & Agarwal, 2004). Antioxidant defence is compromised because of the failure to cope with an increased oxidative demand; thus, it is hypothesised to enhance endothelial cell oxidative damage (Mistry *et al.*, 2008) via the decomposition of polyunsaturated fatty acids in the membranes (Bukhari *et al.*, 2011). Vasoconstriction in PE, resulting from oxidative destruction of nitric oxide (NO) by ROS (Sharma & Agarwal, 2004), could also reduce antioxidative vitamin absorption from the gut (Mohanty *et al.*, 2006).

Aside from the effect of placental insufficiency, oxidative challenges in PIH could partly predispose to the risk of poor foetal outcomes such as PTB, IUGR or SGA, as observed in one third of the cases of pre-eclampsia. This hypothesis could be supported by the presence of excess oxidative stress but inadequate antioxidant defence in the pre-eclamptic foetus (Mistry *et al.*, 2008). Normal birth weight infants were also reported, in most cases, of term PE (Xiong *et al.*, 2002) and even some were born LGA (Xiong *et al.*, 2000), suggesting the presence of a heterogeneous disorder (Xiong *et al.*, 2002) instead of placental dysfunction (Ferrazzani *et al.*, 2011) in affecting the birth outcomes of PIH pregnancies. However, the effect of oxidative stress on the foetus could extend beyond foetal growth and could predispose to later vascular disease. Such an association is supported by Davidge *et al.* (1996), showing endothelial activation with the stimulation of NO in pre-eclamptic foetuses across a wide range of gestational ages, which increases with adiposity and cardiovascular risk factors (Kelly *et al.*, 2010).

B. Early postnatal environment

Infant feeding regime

The trajectory of infant growth is highly dependent on an early infant feeding regime. Human milk has been shown to be an ideal food during infancy, especially during the first month of life (Oddy, 2002). Breast feeding has been reported to protect against later obesity development, which is supported by epidemiology evidence and meta analysis (Horta *et al.*, 2007; Koletzko *et al.*, 2009; Owen *et al.*, 2005). Also, a dose-response association has been shown, indicating a lower risk of adiposity with an increased duration of breastfeeding (Koletzko *et al.*, 2009; Owen *et al.*, 2005).

Several biological mechanisms have been proposed to explain the protective effect of breast feeding against adiposity, such as calorie and protein metabolism, endocrine responses and adipocyte modulations (Heinig *et al.*, 1993; Horta *et al.*, 2007; Lucas *et al.*, 1980). Lower calorie metabolism and protein intake (Heinig *et al.*, 1993; Whitehead, 1995) with a slower early postnatal growth rate (von Kries *et al.*, 2000) in breastfed infants accounted for a decreased risk of obesity compared to formula-fed infants. High blood urea nitrogen resulting from excess protein excretion was suggested to impose metabolic stress in formula-fed infants (Heinig *et al.*, 1993). A greater insulin response, which was observed in formula-fed infants, increased the tendency for fat deposition and early adipocyte development (Horta *et al.*, 2007; Lucas *et al.*, 1980). Indeed, oxidative stress was reported to be involved along those pathway mechanisms (Henriksen *et al.*, 2011; Zhang, Yang & Cohen, 1999). Moreover, a higher amount of nutrients and elements in formula milk implies a higher substrate oxidation than human milk intake. Thus, this strategy produces more ROS by mitochondria, which challenges the infant's immature anti-oxidative defence system (Luo *et al.*, 2006).

From this perspective, we speculate that antioxidant and anti-inflammatory properties of human milk could be the factors, at least in part, that regulate the onset of oxidative stress through permanent modifications in metabolism during the neonatal period, other than counteracting immunological diseases. As mentioned previously, the foetus encounters various oxidative insults *in utero*. At birth, the change from a hypoxic to a relatively hyperoxic environment could enhance the oxidative aggression, as evidenced by the presence of oxidative stress in full-term healthy infants (Friel *et al.*, 2004). This situation is especially worsened in PTB infants because of the immature antioxidant system, incomplete placental transfer of antioxidants and mechanical ventilation (Robles, Palomino & Robles, 2001; Shoji *et al.*, 2003). Thus, it is conceivable that the antioxidant capacity of human milk plays a significant role for resisting the oxidative challenge in infants, although the mechanism remains, for the present, obscure.

A variety of antioxidant components has been reported to be present in human milk and have been shown to provide better antioxidant power than formula milk (Friel *et al.*, 2002). Recently, novel antioxidative peptides derived from enzymatic digestion in human milk were discovered (Tsopmo *et al.*, 2011). The radical scavenging activity of human milk is supported by results showing lower plasma total peroxide, oxidative stress index and urinary 8-hydroxydeoxy-guanosine (8-OHdG: product of oxidative DNA damage) in 1-month-old and 3- to 6-month-old breast fed infants compared to bottle-fed infants (Aycicek *et al.*, 2006; Shoji *et al.*, 2003). Additionally, one study noted that infants fed human milk demonstrated a greater total radical trapping capacity in plasma compared to infants fed formula milk (van Zoeren-Grobben *et al.*, 1994). In parallel with another study, alterations in enzymatic antioxidant defences were suggested to relate to early food intake after birth (Gonzalez, Madrid & Arahuetes, 1995). Thus, the beginning of postnatal infant nutrition is critical in combating diseases.

Poor food choice in infancy and early childhood

A liquid diet or milk feeding is inadequate to meet the demand of a growing infant after the age of six months. Thus, early childhood nutrition is important for determining the intake of essential nutrients and elements for subsequent growth. However, studies indicate the foundation for obesity could be laid when young children are exposed to a poor nutritional practice environments (Fox *et al.*, 2004; Jennings, McEvoy & Corish, 2011).

A recent study conducted in Ireland showed that pre-school children (aged 1-5 years) were served with inappropriate beverages and snacks (Jennings *et al.*, 2011). Another national study in America, the Feeding Infants and Toddlers Study (FITS), raised the concern of a low intake of fruits and vegetables, with an increased intake of high calories and low micronutrient foods among infants and toddlers aged 4 to 24 months. Increasing intakes of sugary foods and sweetened beverages were observed in a majority of infants over 8 months old (Fox *et al.*, 2004). Such early food experiences, especially during the first year of life, persist as future food preferences (Hill, 2002). In other words, unhealthy eating habits could be shaped at this sensitive period, which predisposes individuals to the risk of adiposity. As evidence, a low exposure of home-cooked fruits and vegetables (FV) at 6 months was shown to reduce childrens' FV intake at 7 years of age (Coulthard, Harris & Emmett, 2010). Similarly, early infancy exposure to sweetened water resulted in a heightened sweet preference during childhood (Pepino & Mennella, 2005).

The calorie- and sugary-dense but antioxidant-poor diet during early childhood could exacerbate the background of prenatal oxidant stress. Subsequently, there could be a resulting more frequent adverse programming, thereby partly contributing to the increasing prevalence of obesity. Based on the *in vivo* model, an elevation of urinary 8-OHdG was found in mice that received a vitamin deficient diet and a sweet beverage (Li, Kawai & Kasai, 2007). Furthermore, an increased intake of fructose or sucrose, the common sugars used in manufactured food was shown to induce metabolic abnormalities by disrupting the redox balance and accelerating oxidative stress (Busserolles *et al.*, 2002). A supportive epidemiology study was indicated by an inverse association between fruit and vegetable consumption with oxidative stress markers (Holt *et al.*, 2009). Additionally, a high amount of toxic agents (e.g., arsenic, cadmium and lead) was reported to be present in infants' complementary foods, contributed mainly from their raw materials (Ljung *et al.*, 2011), which increases oxidative generation with a cascading series of cellular signalling and regulation events (Barchowsky *et al.*, 1996; Stohs *et al.*, 2001). Recently, a large body of findings has shown that furan, a heat-induced contaminant that is carcinogenic to humans, is formed in commercial baby foods (Lachenmeier *et al.*, 2010). Such emerging evidence suggests that poor food choices that are pro-oxidative during early childhood could be sensitive targets to oxidative stress programming for the development of obesity.

CONCLUSION

Pregnant women are vulnerable to various oxidative insults in the forms of physiology and chemical and physical. A combination and interaction of different insults could, likewise, contribute to the amplification of oxidative stress. Developmental endogenous (free radicals from cellular metabolism) and exogenous (environmental stimulants) oxidant exposure induces an antioxidant response that is associated with a loss of redox balance in the foetus and neonates. Subsequent programming of the foetal growth increases the risk of chronic disease. Thus, the ability of maternal antioxidant

capacity to maintain the balance of redox status in pregnancy is critically important.

Restoration of antioxidant balance before and during pregnancy could be an early prevention strategy to reduce the prevalence of offspring obesity or the positive adiposity cycle throughout generations. Dietary modification or supplementation with antioxidants and photochemicals could be a priority (Vincent *et al.*, 2007). In fact, the concept of multiple antioxidants is more essential than the single antioxidant and is supported based on their synergistic effects on birth weight (Osorio *et al.*, 2011). However, the availability of a human study on the effect of antenatal administration of antioxidant supplementation on offspring adiposity is lacking. Recently, a study on an animal model has shown that antioxidant supplementation to pregnant Western diet-fed rats decreased adiposity in offspring (Sen & Simmons, 2010). Although there could have been a comparable situation between animal and human models, longitudinal studies in humans are of primary importance for proving that antioxidant restoration in pregnancy through dietary modification or supplementation is practical for offsprings' later health. To translate this intervention into public health messages for obesity prevention, more randomised trials are needed to demonstrate the feasibility and safety.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

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