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Review Article

Oxidative Stress in Pregnant Women and Low Birth Weight

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Abstract

The growth of the child during pregnancy is the result of the interaction of socioeconomic elements, demographic background and health of the family and mother with the inherent biological process. Many factors exert their influence, even before pregnancy, leading to physiological changes that determine some disruptions in the way to full fetal maturation. Oxidative stress is implicated in the pathophysiology of many complications during pregnancy including miscarriage, hypertensive disorders, fetal growth and development disarrays and prematurity. Due to an excess of reactive oxygen species, cellular and biochemical damage make up a severe threat to the well-being of the mother and child, since the protection of the antioxidant system is often deteriorated and is incapable to maintain cellular membrane integrity. Oxidative stress causing this harm has been widely evidenced and poorly understood yet. The potential use of supplementation with antioxidants trying to stop or reverse the oxidative damage, still requires a definition of standard diagnostic criteria and a exhaustive understanding of the mechanism of action.

The aim of this review is to focus the current knowledge on oxidative stress, oxidative stress biomarkers and their relationship with pregnancy outcomes.

Keywords: Pregnancy Outcome; Mother-Child Binomial; Oxidative Stress; Micronutrients; Complications

Introduction

In recent decades, much attention has been paid to the effects of the environment, living habits and food on reproductive health. Epigenetic changes are linked to problems that occur even before pregnancy and during fetal development. The production of free radicals in excessive quantities, so that the dampening systems of the organism are infective, is the cornerstone for the microscopic changes that take place in the cellular structures and in the biochemical mediators.

Maternal and child health is a commitment of all public care systems and is one of the most revealing indicators of the quality of services and community interventions. The identification of the causes that lead to unwanted pregnancy or neonatal and postnatal complications is a permanent objective of the researchers and numerous explanatory literature has been produced over this topic.

The etiology of most frequent pregnancy complications, such as miscarriages, intrauterine growth retardation, or preeclampsia,

and the commonest conditions leading to neonatal complications, including congenital defects, are within the pledges of researchers, public authorities and community groups. Any contribution in the assessment of the existing literature or in the improvement of the actual knowledge about the underlying causes of these concerns, are more than welcome.

Our main purposes are to explore the association of oxidative stress on the etiology of the abovementioned condition, to pinpoint germane data and outline curent knowledge. This article is an extensive literature review on the role of oxidative stress in the pathophysiology of some pregnancy complications with a greater focus on the impact on the baby, particularly in the appearance of low birth weight and its other associated conditions. It is a vision towards the opportunity to comprehend a physiological disturbance of profound impact on reproductive health and define intervention mechanisms that make more favorable prognosis.

Oxidative stress and oxidative stress index

Oxidative stress (OS) is a physiological disturbance resulting from the presence of a certain number of Reactive Oxygen Species (ROS) that the cell is unable to counterbalance, or to cushion. Due to this increase and accumulation, isolated or multiple biomolecular damage occurs, including those to RNA, DNA, proteins and lipids. OS is recognized as a strong tissue-aging factor and promoter of the onset and/or prevalence of a variety of diseases. The intensity or the Oxidative Stress Index (OSI) can be a useful tool to link the onset of systemic diseases in adult [1] and up to their course and severity, as occurs in essential arterial hypertension and type 2 diabetes mellitus, according to reports by Núñez-Sellés., *et al.* and Núñez-Musa., *et al*. [2,3].

ROS and reactive nitrogen species (RNS) participate in several important signaling pathways that help regulating many cell tasks and functions, like growth, differentiation, mitosis, extracellular matrix production and breakdown, apoptosis, oxygen sensing, and inflammation and promote endothelial dysfunction by oxidation of crucial cellular functions. The ROS act as both signaling molecules and as mediators of inflammation. The ROSs can combine with nitric oxide to form RNS which, in turn, provokes the so called nitrosative stress, an associated disturbance within the OS spectrum that adds more inflammation [4]. It is also recognized their role in the immune system against some pathogens microorganisms [5].

The antioxidant adaptation is responsible for the signal formation and transport of the appropriate antioxidant to the site of excessive free radical and prooxidant production. Antioxidant enzymes decompose lipid hydroperoxides to alcohols, and reduce hydrogen peroxide to nontoxic substances [6,7].

The identification and development of specific biomarkers of OS (BOS) are important, particularly in cardiovascular, neurodegenerative, cancer, immunological, metabolic and respiratory diseases. The discovery, titration and correlation of biomarkers with varied health situations in the population can contribute to the early recognition of the physiological disorder.

OS can be quantified by direct titration of ROS, by measuring the resulting biomolecular damage or by determining antioxidant levels. The first is the ideal method, but the instability of many ROSs and the difficulty of measuring them directly creates many problems of safety, cost and opportunity when using them. In daily practice, it is preferred to quantify the biomolecular damage.

The samples to determine the BOS are usually simple and easy to obtain (cell scraping, urine sample, blood drop and saliva sample). Although there are direct techniques for measuring ROS and other free radicals, indirect techniques are the most common, by which ROSs are captured by a suitable reagent to form a stable chemical entity which is then analyzed by gas, spectrophotometry, immuno-enzymatic and chromatographic techniques. Most BOS used for assessment are highly stable and provide very reliable information to estimate the presence and degree of OS. The measurement of antioxidant enzymes and other molecules of the RedOx cycle is equally effective, although slightly less than that of the titration of damaged biomolecules. However, due to the need to evaluate specific cellular metabolic processes, there are tests that measure the specific activity of some antioxidant enzymes, such as catalase and hyperoxydismutase. Other measurements are used to assess the hydroxylation of salicylic acid or the detection of nitric oxide radicals by colored final compounds. Several studies on the involvement of OS in specific diseases, as well as the determination of BOS for each case, have given more reliability to the interpretation of its role as predictive tests and/or follow-up of diseases [8].

However, it will be necessary to measure different biomarkers to establish the association of OS with the appearance and development of defined pathological processes, as well as the rational to implement a therapy and a follow-up system for routine use. Due to the complexity of OS-associated diseases, a single BOS will not be reliable to support clinical diagnoses. Therefore, it is necessary to count on a group of BOS, not only for the correct diagnosis, but also for the safe monitoring of the evolution of the disease (Table 1).

Type of measurement	Biomarker		Detection	Sample
Direct	DCFH-DA		Flow-cytometer	Platelets and leukocytes
	DHR123			Leukocytes
	DAF-2-DA			
	DAF-FM			
	d-ROMs			Serum
	C11-BODIPY$^{581/591}$			Platelets, leukocytes granulocytes
Indirect	4-HNE	Lipid oxidation	ELISA	Urine and plasma
	MDA		HPLC	
	TBARS		ELISA	
	F2-IsoPs		Gas-chromatography ELISA	Biological fluids
	DNPH	Protein damage	Colorimetric	
	AOPP			
	8-OHdG	DNA damage	ELISA	Blood and urine
	SOD Catalase	Enzymatic anti-oxidants	Colorimetric Western blots	Biological samples

Table 1: Most used biomarkers of oxidative stress and their detection methods.

DCFH-DA: 2′-7′Dichlorofluorescin Diacetate; DHR123: Dihydrorhodamine 123; DAF-2 DA: Diaminofluorescein-2 Diacetate; DAF-FM: Diaminofluorescein-FM Diacetate; d-ROMs: Reactive Oxygen Metabolites; C11-BODIPY$^{581/591}$: Oxidation-Sensitive Fluorescent Lipid Peroxidation; 4HNE: 4-Hydroxynonenal; MDA: Malondialdehyde; TBARS: Thiobarbituric acid reactive substance; F2-IsoPs: F2-Isoprostanes; DNPH: Dinitrophenylhydrazine; AOPP: Advanced Oxidation Protein Products; 8-OHdG: 8-Oxo-2′-Deoxyguanosine; SOD: Superoxide Dismutase

Therefore, which BOS and methods to measure them, in order to assess oxidative status, are best? In clinical practice, sampling should be based on the objective of the assessment as much as of the clinical purposes. Actually, no single parameter has yet been standardized nor specific tools have been agreed, despite the many clinical trials proving the effectiveness of a procedure like this as a coadjutant in medical practice [9]. The ever-present and nonspecific nature of OS demand to measure a whole panel of BOS instead of a single parameter, as this improves the possibility of a relying on one true positive result [10]. In addition, so very often significant discrepancies in the study designs, type of sample, target populations, and analytical procedures contribute to dissenting data in the different trials and reviews.

There have been many attempts to design an integrative approach to obtain a comprehensive score that provides a higher sensitivity to quantify the OS in relation to the onset or worsening of some diseases [1,2,4,11]. The measurement of a comprehensive redox status includes, more commonly, the Oxy-Score and the OSI. The former is a summary index of oxidative stress, computed by combining plasma free and total ROS levels/ROS-induced damage. The OSI is the ratio of total oxidant status to total antioxidant status, which simultaneously reflects the oxidative and antioxidant status in the samples taken from clinical cases, therefore, may provide a stronger parameter to evaluate the OS and its relationship with the disease investigated.

The OSI was initially proposed in 2003 by Harmaa., *et al.* [12] and has undergone modifications since then, but still preserves the core of its equation in that it is a ratio between Total Oxidative Capacity (TOC) and Total Oxidant Status (TAS), as per the following formula

$$\text{OSI (AU)} = \frac{\text{TOC}}{\text{TAS}}$$

Where OSI is expressed in arbitrary units (AU), TOC in µmol H2O2 Eq/L, and TAS in µmol Trolox Eq/L. The result is usually presented as percentage ratio.

At present, it is not possible to ignore the role that the OS plays in the pathogenesis of various diseases and, even, in their evolution. OS is closely related to physiological activities that determine highly complex cellular functions. A method to measure with cer-

tainty and predictive value is around the corner and, once reached, will be one of the most useful tools for medical use.

The child and the mother

The monitoring and control of pregnancy, childbirth and breastfeeding includes a series of coherently well-articulated strategies that seek to ensure the well-being of the mother-child binomial from the moment of conception. The guarantee of a comprehensive care for the binomial seeks to minimize the risks associated with pregnancy and childbirth and should include, programmatically, a diet containing micronutrients and essential compounds, taking into account that for years it has been known the favorable effect of an adequate dietary balance in the pregnant women [13]. In addition, for decades it has been recognized that the loss of dietary and nutritional balances relates to the onset of OS and plays a very decisive role in the pregnancy health and in the baby development [14].

There is a growing interest in defining the close relationship between OSI in pregnancy and the incidence of low birth weight (LBW), especially in relation to the pathogenesis of placental disease, where pathological changes are of deep impact in the newborn progress and stability. For years, several studies have proposed early supplementation alternatives with antioxidants as a preventive adjunct to the development of pregnancy complications, including OS, to help reduce the incidence of LBW and contribute to decreasing the level of risk to nosological sequelae in adult life, like cardiovascular diseases and type 2 diabetes mellitus [15,16].

Throughout intrauterine growth, socioeconomic elements, demographic and health background of the family and mother interact, as well as other determinants, to exert their influence, even before pregnancy, over physiological changes. Within these factors, we find the nutritional habits, lifestyle, environmental toxins, reactants, and the use of certain substances and medicines. All of them are able to affect, not only the health of the child before and after birth, but also his future health as an adult, due to the epigenetic changes that derive from those interactions, in which the OS plays one of the most important roles.

Low weight, prematurity, intrauterine growth restriction (IUR) and congenital diseases are conditions of high impact on neonatal health, causing high rates of infant morbidity and mortality. Modern biotechnology has favored a greater survival of these newborns and at present, there are reports of highly successful results in newborns with weight less than one kilogram [17]. However, the state-of-the art management for fatal complications in underweight or premature children remains a stigma for many countries with less access to cutting-edge technology or high-cost equipment. For these populations, the search for preventive measures of easy access and low cost remain the best strategies.

In some countries where the use of up-to-date technologies is limited universally, infant mortality can reach levels as alarming as 27 per thousand live births, with projections of up to 40,000 deaths in neonatal age for a determined time range [18]. LBW and IUR are prevalent and linked to most neonatal deaths, along with other major causes relate to prematurity and with intrapartum complications. Infections account more than a third of all deaths, pre-term 28%, and birth asphyxia 23% [19]. There is some variation between countries depending on their care configurations and for low income nations and socially vulnerable populations, these numbers may not apply. In some countries, for instance, most of those more than 40,000 neonatal deaths will be connected to LBW and/or IUR, with or without prematurity, which in turn may be associated with undercurrent infection or congenital disease, thus raising risk and mortality rates much higher. First world countries face different most common causes.

The tissues of the newborn baby are very labile for the purposes of OS, especially because neonate metabolism is quite dynamic and changing. This condition favors a kind of susceptibility that potentiate the damaging effects of free radicals. Although more in-depth studies with a wider range of cohorts are still needed, many experiences have shown a connection between the effects of OS on the development and outcome of the pregnancy. Few publications validate the role of BOS in the early diagnosis of neonatal outcome. Negi., *et al.* found an association between BOS and enzymatic/non-enzymatic antioxidants in the cord blood of preterm LBW neonates, suggesting that increased OS is a causative factor [20]. A study conducted by Mert., *et al.* in 24 patients with preeclampsia, 20 patients with IUR fetus and 37 healthy pregnant women, concluded that increased OS and antioxidative defense mechanisms may contribute to disease processes both in preeclampsia and IUR [21]. Even in cases where BOS were not conclusive, some authors have even advised the use of them in combination with biophysical parameters and maternal characteristics as a more useful approach to early recognition of potential complications [22].

The quality of life of a pregnant woman improves markedly with the selection of food for its value, rather than its quantity, provided that the approach is aimed at reducing micronutrient gaps that would lead to imbalance situations such as the one that character-

izes the OS[14,15]. Over the past 40 years, efforts have increased to expand the range of nutritional coverage, especially for the population at potential risk, for instance, the pregnant women and neonates [23]. Some researchers have recommended the inclusion of specific micronutrients to prevent or manage the OS and the determination and follow-up of the OSI is postulated as a way to prevent unwanted outcomes or to assess the occurrence of potential pathological events, both in the mother and in her baby [14,24,25]. Similar experiences moved, more than 30 years ago, to incorporate some nutritional principles or dietary components in the food routine of pregnant women for their preventive effect of pathologies related to fetal development, as was the case with folic acid and vitamin A. Similarly, oligoelements such as selenium, copper and zinc are part of the molecular structure of some of the antioxidant enzymes, so these micronutrients are an important part of metabolic reactions. Both, deficiency and excess may be involved in damage to various organs and tissues of the mother and fetus [26,27].

Micronutrients, oxidative stress, pregnancy and newborn at risk

The degree of OS has been very closely interrelated to the risk of developing hypertensive states of pregnancy [15,28], which supports the hypotheses about the use of micronutrients with antioxidant power and their possible participation as protectors in these pathologies or in pregnant women at risk [29]. Many antioxidant enzyme factors depend on essential nutrients. For example, the expressions of glutathione peroxidase and thioredoxin reductase depend on adequate amounts of selenium; the expressions of superoxide dismutase depend on a satisfactory supply of copper and zinc and the activity of glutathione reductase depends on a sufficient consumption of riboflavin. OS leads to high concentrations of lipid peroxidation products, which are linked to the pathogenesis of some conditions, for both the child and the mother [30], since they can generate a battery of free radicals and cause protein modification in a stable process of oxidative damage even under physiological and environmental conditions. Such damage is interconnected to the progressive accumulation of errors at DNA level that govern one or more factors in protein oxidation, ultimately altering the biological functions of the protein-dependent cell, such as enzymes and, additionally, causing chromosomal damage that can be reflected in congenital malformations [31].

Copper contributes to the formation of red blood cells and the maintenance of blood vessels, nerves, immune system and bones. It plays an important role in the detoxification of oxygen radicals in the cell cytoplasm, although it is thought that also catalyzes the formation of free radicals, including hydroxyl radicals, thus contributing to the OS status of pre-eclampsia. Indeed, since the middle of the last century copper was seen as part of the chain of biochemical events within the pathogenesis of preeclampsia and, more recently, it was connected significantly with its degree of severity [32].

Selenium is associated with the protection of tissues against the effects of OS, especially those involving peroxidized lipids, as well as in the maintenance and modulation of processes of the immune system and the resistance to toxicity by heavy metals. Therefore, its deficit is one of the indicators of OS. The deficiency of this trace element can cause difficulty to achieve fertilization and can promote complications in pregnancy, such as abortion, in the postpartum and the neonates, besides the potential impairment of the immune system [33,34]. A Polish study in 410 mother-child pairs showed that prenatal selenium status was associated with child psychomotor abilities within the first years of life and fetal nervous system development [35]. Low selenium concentrations are associated with LBW and small-for-gestational age babies, maybe linked to a low thyroid function [36], and even the placental selenium concentration selenium can serve as a predictive value test for LBW [37]. Long standing effects of selenium deficit may result from a permanent damage on genes, due to harm in developmental programming [38]. Like other micronutrients, selenium requirements in pregnant women increase so that, at present, the tendency is to ensure an adequate supply, through a properly balanced diet or through supplements, even more if the presence or risk of OS is known.

Zinc is an essential component for a large number of enzymes, very similar biochemically to magnesium. It participates in the synthesis and degradation of carbohydrates, lipids, proteins and nucleic acids, as well as in the metabolism of other micronutrients, such as phosphorus and copper, and is involved in the development of the skeleton, nervous system, brain and reproductive organs. Although it is virtually distributed throughout the body, being the second most abundant transitional metal after iron, it is mostly concentrated in the brain, bones, kidneys and liver. Its wide and widely spread biological role in the organism includes the metabolism of RNA and DNA, the transduction signals and the genetic expression, and its activity initiates from the very beginning of conception [39]. Zinc participates in the regulation of apoptosis, is a modulator in great part of all body proteins, and in the functions of T helper lymphocytes [40,41]. The homeostasis of zinc is determi-

nant for the nervous system, since its alteration is related to serious disorders of synaptic transmission and induces neurotoxicity as its deficiency-promoted OS affects mitochondria [42].

Zinc shortage affects more than two billion people worldwide. It is a cause or cofactor in a considerable number of health problems such as stunting and sexual maturity impairment in children. Zinc associates to an increased susceptibility to infections, particularly diarrhea, and may even reverberate as early as the embryonic stage with further complications in childbirth [43]. Failures in fetal growth and linear growth from preschool age, have usually improved with dietary supplementation of zinc, whenever detected on time [44]. It is possible that the decrease in the concentrations of this micronutrient affects the antioxidant action in pregnancy.

In short, alterations in the availability of zinc in the diet of the pregnant woman, can lead to pathophysiological effects related to the intensity of OS that lead to IUR, LBW, serious central nervous system disorders and infections.

Discussion

Birth weight is probably the commonest and simplest resource to assess the nutritional and metabolic conditions of the mother, as well as fetal development during pregnancy. LBW is a condition that can be seen as both a biological and a social threat, largely because globally and in all population groups it is the single most determining factor of the newborn's chances of surviving and having healthy growth and development.

As maternal and child health conditions are related to the social reality and public care, the technological advances may not be of help especially in populations living under vulnerable situations. That is why, biological, social, and care-related aspects should be considered in the mother and child wellness, since differences in exposure to risk or triggering factors may lead to physiological disturbances like OS of variable impact. Living and work conditions, food availability, types of behaviors, lifestyle, and the health system, particularly if prenatal care is deficient, must be understood as part of the most important determinants of health. All these factors, in one way or another, affect the quality and quantity of food that a pregnant woman and/or her child should receive.

Although the LBW was recognized as a health concern centuries ago, it was only a little over 60 years ago that the World Health Organization (WHO), in its 1950 Technical Report, coined the term and defined its characteristics. WHO stated that a newborn with weight between 1000 and 2 499 g or between 2.2 to 5.5 pounds faces exponential hazards of complications. Still in the present, this definition remains a critical aspect in the field of reproductive and social health, even for industrialized countries. Since the late 1970s, the LBW was assumed as a situation that required comprehensive attention with joint strategies, protocol and homogenization of criteria, given the high incidences found in all live births in that decade. By then, there was a high proportion of neonatal deaths, related to prematurity and LBW in conjunction with maternal malnutrition [45]. Although the interventions were intensified in order to reduce the incidence and effects of LBW, did not change some realities because still in many countries the vast majority of neonates were not weighed at birth or were the product of non-institutional births [46].

LBW and prematurity, especially if the latter is accompanied by LBW, make up the health indicator with the highest epidemiological and predictive burden of morbidity and mortality in children under one year and, in general, in all mortality below five years. Although it has long been recognized that the frequency of children with LBW is proportionally directly related to perinatal fatality, making it the most accurate indicator of neonatal prognosis, in recent years, ultramolecular medicine and genomic sciences have opened the field to understand and face this condition from a more microstructural point of view [47]. At these levels, it is precisely where the most striking changes take place in the cellular structures of the fetus subjected to the effects of micronutrient deficiencies and subsequent OS.

The decrease of the incidence of newborns with LBW is a development goal for any nation, whose main purpose is its contribution to the reduction of overall infant mortality, since this is the component of the highest impact. Life expectancy beyond the first year and the quality of child development have been improved in many countries, thanks to the fact that they have managed to drastically reduce infant mortality and have done so through constant and effective interventions in maternal and childcare, as much as in the reduction of prematurity, LBW and IUR. Effective vaccination and sanitation campaigns add to all these strategies.

Children with LBW include those born on term with low weight for gestational age, usually described as having nutritional deficit "in utero", with intrauterine growth delay, or as small-for-gestational age. Although premature babies can appear with low weight on the general scale, for their gestational age, they may be normal but carrying the risks of prematurity, which are similar to the LBW

group. The greater or lesser impact will greatly depend on the target population concerned and the degree of maturity at childbearing. In general, LBW will be the result of inadequate intrauterine growth, too short a gestational period, or both.

LBW-related conditions as risk factors, mostly serve to identify groups at risk, but knowledge of the root causes has remained quite controversial despite technological advances and new medical alternatives for research.

For example, it is known for several decades that inadequate maternal diet is a causal factor for inadequate fetal growth, with expressions of varying importance in each population, some of which reach alarming levels. Only since the end of the last century were micronutrients seen as elements of high impact within the pathogenesis of LBW, beyond the macro conceptualization "of diet and pregnancy" and as part of therapeutic solutions. While some sources do not report tangible benefits with the use of micronutrients during pregnancy as a mechanism to reduce LBW and other complications [48], most of these did not take into account aspects related to the benefits of micronutrients in reducing OS and, in other cases, they were targeted as dietary substitutions. However, in conditions specifically related to the health of the mother-child binomial that do not refer to pathologies of pregnancy, such as OS, whose presence is documented as an important risk factor, the effect of micronutrients complementary to the pregnant woman's dietary protocol has shown to be favorable for the course and outcome of pregnancies in several casuistic [14,25,49].

Another important risk factor in the appearance of LBW is multiple pregnancies, whose increased frequency is associated with the rise of assisted fertilization [50]. In some populations, this may not be of great concern regarding the productive health, but in most cases the vulnerable groups, where there is greater poverty and lower health coverage, multiple gestations is a major public health worry. In these two scenarios, OS is able to be present since preeclampsia is a common complicating syndrome in multiple gestations, due to that OS affects the placenta in such a way that it causes a reduction in antioxidant enzymatic protection and a placental endothelial dysfunction, all connected to its pathogenesis [16,51]. In addition, multiple pregnancies and/or placental hyperplasia are circumstances that can be assessed by titration of biomarkers for OS as early as in the first trimester of pregnancy [52].

Every year, 20 million or more children are born with LBW and 95% of these births occur in undeveloped countries [53]. Many of these children will have developmental disorders, neurological or psychological morbidity, and some will suffer, in adulthood, coronary, renal and respiratory diseases that link to the past prenatal/neonatal history [54]. Additionally, the recent association of IUR, prematurity and LBW with Sudden Infant Death Syndrome has sparked greater interest in addressing low weight prevention with more inclusive strategies [55].

Children with LBW have an altered immune function, poor cognitive development and high risk of developing diarrheal and respiratory diseases, where micronutrient deficiencies and OS play a determining causal role. Of these that survive, many have little chance of reaching their true growth potential and end up being classified as short stature. Poor nutrition begins in utero and extends throughout the life cycle of an infant, which amplifies the health risk and increases the likelihood of future pathological conditions. The range of disturbances include weakening of the antioxidant defense system, failure in the quality of metabolic processes, exacerbations and loss of control of regulatory mechanisms in chronic respiratory diseases, limitations in the ability to cushion inflammatory activity and decreased metabolic regeneration. Therefore, in pregnancy it is particularly important to recognize that the effects of OS act from the very beginning and are more evident from the second trimester of gestation, reaching its peak between 27 and 40 weeks, precisely when metabolic and oxygen requirements skyrocket due to the increased rate of fetal needs.

In the last weeks of gestation, within the process of food storage, micronutrients such as copper, zinc and selenium, pass to the fetus from the maternal blood via placenta, so that situations like maternal malnutrition or placental disease close related to shortage of these elements, will be the breeding ground for a progressively deleterious OS causing irreversible damage.

Conclusion

The data accumulated at present show that alterations in the serum concentration of antioxidants during pregnancy could be the cause of multiple changes in the mother and child health. Early intervention with accurate and reliable measures to identify OS and to determine OSI is an excellent and effective resource to prevent unwanted outcomes in pregnancy. A critical evaluation and the adaptation of methodologies to choose the most adequate biomarkers in order to use them as predictive of the pregnancy outcome should be of particular interest in some health settings. Preventive actions at any time of pregnancy, with particular attention to its second half, should be accompanied by a general orientation with respect to early diagnosis of OS and favor a nutritional supplemen-

tation aimed at combating it. It may beneficial to establish nutritional schemas including the supplementation of antioxidants and micronutrients in a programmed and universal way, as part of health policies, even in the absence of robust and large-scale trials.

Conflicts of Interest

The authors declare no conflict of interest.

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