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Free Radicals and Antioxidants Status in Pregnancy: Need for Pre- and Early Pregnancy Assessment

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Abstract In normal pregnancy, free radicals are still generated. These free radicals are beneficial to the body at physiological levels, but when their production rates overwhelm the synergistic actions of available antioxidants, several deleterious or harmful conditions may ensue, including adverse pregnancy outcomes. These outcomes have been variously described. We reviewed the roles of free radicals on pregnancy outcome, and the benefits of optimum levels of antioxidants during pregnancy, to assess the possible influence of these parameters on outcomes of uncomplicated pregnancies. This may help to understand the need for pre-pregnancy and early pregnancy assessment of antioxidant status of women. Our research words included, among others, free radicals in pregnancy, effects of free radicals on pregnancy outcomes, oxidative stress in pregnancy, antioxidant status of pregnant women and actions of antioxidants against free radicals. We are of the opinion that the outcome of an uncomplicated pregnancy may be dependent on the amount of free radicals generated during parturition and the antioxidants status of the pregnant woman. We therefore advocate for pre-pregnancy and early pregnancy assessment, as well as establishment of reference values of oxidant and antioxidant parameters in normal pregnancy in every locality.

Keywords Free radicals, Antioxidants, Uncomplicated pregnancy, Pregnancy outcome

1. Introduction

During biochemical or physiological processes in the body, several free radicals are produced, including reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive chloride species (RCS). The physiological processes involved in free radical production have been variously described, including absorption of radiant energy, [1] oxidation-reduction reaction, [2] activation of macrophages, [3] inhalation of transition metals (like iron and copper) from ambient air, [4, 5] sensitization of carotid body by reduced oxygen concentration – hypoxia, [6, 7] expression of cell adhesion molecules, [8] redox-mediated amplification of immune response, [9] induction of apoptosis, [10-12] oxidation of dopamine, especially in the central nervous system, [13] extensive exercise [14] and pregnancy[15]. Ordinarily, free radicals are produced mostly as a defence mechanism, and used by the body in various ways to fight invaders, especially microorganisms. However, from the physiological point of view, it is now understood that not all free radicals are produced in defence, but also for other benefits. For instance, nitric oxide (NO), which is an RNS, can be used as a regulator of vascular tone and as a messenger in the central nervous system; others may regulate gene expression, monitor oxygen tension in the control of ventilation and erythrocyte production, cause signal transduction from membrane receptors, and induction of apoptosis, as well as being involved in cell differentiation [11, 16, 17]. The ability of these radicals to kill invading organisms means that they are capable of damaging normal tissues, mostly through biochemical changes (oxidative damage). An imbalance between the generation of free radicals and protection against them, results in oxidative stress [18]. This is characterized by increased concentration of oxygen and non-oxygen-derived products that provoke critical, and sometimes irreversible, cell injury [19]. Incidentally, even when produced at normal levels, some of these free radicals still cause damages to the body cells. This is because, under physiological condition, the balance between these generated free radicals (oxidants) and the defences against them lie slightly in favour of the radicals. Therefore, this life giving and life saving oxygen can initiate deleterious or harmful effects. Thus, more than three decades ago, oxygen was described as a potential toxic substance [20] and the toxicity is actually attributable to its conversion to superoxide and other forms of reactive species. This led to the observation that the metabolism of oxygen, though central to life, produces reactive oxygen species that have been implicated in processes as diverse as cancer,

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cardiovascular diseases and aging [21].

In pregnancy, these adverse effects of reactive species can alter the progress of pregnancy, development of the foetus and state of the infant at delivery. We reviewed different publish journal articles and website-posted articles on the effects of reactive oxygen species/free radicals on pregnancy, and the activities of antioxidants against such radicals for the benefit of pregnant women, foetuses and pregnancy care-givers. Our key/search words included 'free radicals/ reactive species in pregnancy', 'factors causing untoward pregnancy outcomes', 'indicators of pregnancy-induced illnesses' and 'effects of oxidative stress or free radicals on pregnancy outcome'. Others include 'actions of antioxidants against free radicals', 'antioxidants status of pregnant women', 'prevention of untoward pregnancy outcome using antioxidant supplements', and 'benefits foetuses and infants derive from antioxidants supplementation'. Over 85 articles were retrieved but those that did not have direct reference to the subject matter and those that were quite old (15 years and above) and were not extra-ordinarily important to the topic were not considered for referencing.

2. Free Radicals in Pregnancy

Pregnancy is a physiological condition. In normal pregnancy, the earliest stages of development take place in a low oxygen environment – physiological hypoxia of early gestational sac, which is however beneficial because it protects developing foetus against the deleterious and teratogenic effects of ROS [22]. However, as gestational age increases, a lot of physiological changes occur, due to increased demands and changes in plasma volume. These changes range from decrease in vitamins and minerals, especially antioxidant vitamins, [23, 24] to decrease in macro and micronutrients, as well as haemoglobin levels [25, 26]. Moreover, because of the mitochondria-rich placenta, pregnancy is a condition that favours increased production of ROS, [27] and this peaks by the second trimester of pregnancy, ending what appears to be a vulnerable period of foetal health. These changes account for the dynamic changes in multiple organ systems that lead to increase in basal oxygen consumption [15]. Hence, during this gestational period, significant increase in oxidative stress markers are seen as indicators of pregnancy-induced hypertension (PIH), otherwise called preeclampsia [28, 29, 30, 31]. Thus, exaggeration of oxidative damage is considered important in pregnancy complications, including the breakdown of syncytiotrophoblast [32]. In addition, pregnant women are greatly predisposed to malaria parasitemia and other infections and infestations. This is well pronounced in low socio-economic rural areas of developing countries where symptomatic and asymptomatic malaria parasitemia among pregnant women are very high [26, 33]. All these conditions generate enormous free radicals, which are dangerous to the foetuses. Earlier studies, [34-36] have shown that pregnant women, especially primigravidae and secundigravidae, have low immune functions, probably due to enhanced catabolism of tryptophan by maternal dentritic cells. This leads to down-regulation or suppression of T-mediated or adaptive immune response. Though this low immunity is required by these pregnant women to tolerate genetically different foetal tissues, [37] it ends up increasing the susceptibility of these women to infections. Malaria infection and other stress-causing factors in pregnancy have been implicated in uncountable perinatal and maternal illnesses including abortion, stillbirth, low birth weight and even death [38-40]. These illnesses are mainly due to generation of free radicals. Free radicals have also been implicated in pre-eclamptic toxaemia (PET) in pregnancy, hence their activities are linked to some foetal abnormalities and other disease conditions in pregnancy, and even failed reproductive performances like infertility, miscarriage and diabetes-related congenital malformations [32, 41, 42].

3. Antioxidants in Pregnancy

Antioxidants are substances or molecules that are capable of reducing or stopping the effects of oxidants. These substances include, among others, micronutrients like some vitamins and trace elements, some metallo-enzymes like catalase, superoxide dismutase (SOD) and glutathione peroxidase, as well as phytochemicals like carnitine, carnosine and polyphenols. Many antioxidant micronutrients have been found to improve immune functions in many animals including human beings, and they act by donating electrons or binding directly to the free radicals, or interrupting the chain reactions involved in cell damage [43, 44]. They include vitamins A, C and E, and trace elements like copper, manganese, zinc and selenium. There has been a recent resurgence of studies on vitamin supplements for pregnant mothers, aimed at not only reducing intra-uterine, foetal and neonatal infections, but also pregnancy complications such as pre-eclampsia, premature membrane rupture and preterm birth. [45-47] In some studies within the urban areas of south eastern Nigeria, [23, 24] there was significant reduction of vitamin C in pregnancy. These studies showed progressive reduction of vitamin C, and a positive correlation between vitamin C and serum iron over gestation, implying that vitamin C deficiency can also lead to iron-deficiency anaemia. In other previous studies from other countries, [41, 48] low levels of some lipid-soluble antioxidants were found in pregnant women with pre-eclampsia, while deficiencies of diet-derived antioxidants were thought to predispose to foetal and childhood slow or abnormal development. Specifically, zinc deficiency in females was found to cause, among other things, many abnormal pregnancy outcomes including frequent abortion, prolonged gestation, teratogenicity, stillbirth, difficulty in parturition, pre-eclamptic toxaemia and low birth weights of infants, while selenium deficiency is implicated in infertility, abortion and retention of placenta [49]. Based on this, a drop in total antioxidant status during pregnancy was concluded following significant decrease in plasma and whole blood selenium and selenium-dependent glutathione peroxidase activities during gestation [50].

Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are the most prominent natural antioxidant enzymes that can eliminate ROS [51]. Some of these antioxidant enzymes are activated by the presence of metal ions, while in some metal ions have structural roles. For instance, the presence of copper in superoxide dismutase (CuZnSOD) confers antioxidant property to the enzyme while zinc has structural role to play, thus erythrocyte CuZnSOD is known to be diminished in copper deficiency [48]. Manganese is also known to activate SOD and other enzymes responsible for the utilization of several key nutrients, including vitamin E – an antioxidant itself [52]. Natural selenium-containing antioxidant enzymes - glutathione perioxidase and thioredoxin reductase, are known to have the potential to reduce the effects of free radicals on the aging process and also protect neutrophils, macrophages and other tissues from free radicals intended to destroy pathogens in the fight against inflammation [44]. Hence, neutrophils with reduced glutathione peroxidase activity due to selenium deficiency were found to be unable to defend themselves against free radicals they release onto pathogens [53, 54].

Antioxidant phytochemicals are non-vitamin, non-mineral antioxidants obtained from plant sources especially fresh fruits and leafy vegetables. Since 1980s, public health recommendations have emphasized the health benefits associated with the consumption of fresh fruits and vegetables [55]. Epidemiological and animal studies linking the consumption of plant foods with major reduction in the incidence of lung cancer and other malignancies, which are products of oxidative stress, give ample support for this recommendation [56]. This stemmed from the fact that people who consume more vegetables and fruits show significantly superior health compared to those eating the least, especially in regard to lower rates of cardiovascular disease and cancer. Some of these vegetables and fruits also contain other antioxidants, especially vitamin antioxidants whose functions in pregnancy have been variously described [57-61]. Unfortunately, these fruits and vegetables which are produced from our rural areas are not consumed by the producers, but are transported to the nearby urban areas for paltry financial return [62].

From the foregoing, it is understood that even uncomplicated pregnancy favours increased production of free radicals, [27] and therefore oxidative stress. These free radicals make pregnant women to be vulnerable to infections, which in turn join forces with oxidative stress to cause uncountable perinatal and maternal illnesses [38-40] and even congenital malformations [41, 42]. On the other hand, low levels of antioxidants have been reported to cause many adverse pregnancy outcomes and even foetal and childhood slow or abnormal development [41, 48, 49]. Therefore, pregnancy care should include programmes to reduce free radical production, and increase antioxidants levels in those pregnant women.

4. Stating the Case

The major condition causing pregnancy complications in our environment is malaria parasitemia, with high prevalence reported in different parts of Nigeria [26, 33, 63, 64]. The effects of symptomatic malaria parasitemia on production of free radicals (oxidative stress) have been documented [65, 66]. Subsequently, we reported non-significant changes in serum levels of some indicators of oxidative stress in asymptomatic parasitemia [15]. Normally, pregnancy is associated with high metabolic demand. This leads to reduced macro and micronutrients in normal pregnancy, provoking oxidative stress. This results in mobilization of antioxidant defences, and subsequent reduction in the levels of these antioxidants [62, 67]. Previous study has shown that the micronutrient status of a pregnant woman is an important determinant of foetal growth and survival, [68] and multiple micronutrient deficiencies during pregnancies are said to be common in developing countries, [69] including Nigeria. Yet maternal malnutrition, which is related to the continued adverse feto-maternal outcomes, has not attracted enough attention from the authorities, [70] while much energy and resources are channelled into HIV/AIDS prevention and treatment. Since poor nutrition and micronutrients deficiencies are known to aggravate malaria anaemia and other impacts of malaria on pregnancy, [71, 72] there is absolute need to streamline the nutritional requirements of our pregnant women in order to guide our pregnancy care-givers accurately on the use of supplements. Thus, it has been advocated that more attention be directed to the improvement of the nutritional status of our rural populace to improve the health and immune status of the pregnant women therein [73]. Therefore, studies geared towards understanding the effects of normal pregnancy on antioxidant micronutrients, and their correlation with one another during parturition are of paramount importance in this environment. As at now, even pre-pregnancy care, an aspect of obstetrics practice, has not received the needed attention [74]. Likewise, basal levels of oxidant and antioxidant parameters in normal pregnancy, that should form the guidelines for the choice of supplements, have not been well elucidated. This calls for concerted efforts by our scientists to take in-depth look at the pre-pregnancy conditions of our women, and factors that may affect pregnancy outcomes in apparently normal parturition, including general nutrition and specifically, antioxidant micronutrients. The later will form the basic values for comparison in cases of pregnancy complications where diagnoses are usually urgently needed. It will not only help our pregnancy care-givers in their choices of supplements but be a guide on dietary advice during pregnancy. Presently, most of the documented studies from our environment, [15, 23, 24, 70, 75] which also involved few antioxidants in each case, were from urban areas, with the exception of one [62]. So far, there is dearth of documented comprehensive studies on oxidative stress indicators and micronutrient antioxidants in pregnant women from our rural areas, where inadequate and/or unbalanced nutrition is the order of the day, and where malaria parasitemia and other infections are threats to every pregnancy. Therefore, there is an overriding need to establish the reference values of these parameters in normal pregnancy within each locality. This will help to draw a good conclusion on the influence of oxidative stress on pregnancy outcomes, and also help to detect when a particular pregnancy is in danger due to oxidative stress. By this, we would have taken a right step to solving most feto-maternal problems for the attainment of Millennium Development Goals (MDGs).

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