Oxidative stress can be defined as a state of disrupted balance between reactive oxygen species and the mechanisms of detoxification and repair. Reactive oxygen species (ROS) are formed in every living cell during the physiological process of breathing, and a molecule of ROS contains an atom of oxygen with an unpaired electron. During a normal pregnancy, oxidative stress enhances antioxidant mechanisms that are capable of reacting by way of enzyme activity and non-enzyme free radical deactivators. However, pregnancy is also a state in which this adaptation and balance may be easily disrupted. There is strong evidence that a chronic inflammatory reaction combined with the presence of a local oxidizing environment may play a vital role in the etiology and development of complications during pregnancy. In late pregnancy, damage to DNA (especially when it is caused by oxidative stress) is associated with pre-eclampsia (PE), intrauterine growth restriction (IUGR), and the death of mothers in developing countries; it largely determines pregnancy-related susceptibility to diseases. The referential values of ROS and NOS and their minimal and safe concentrations or physiologically beneficial concentrations are yet to be determined. The measurement of oxidative stress in vivo is perceived as controversial, as the sensitivity and specificity of various oxidative stress markers is unknown. The measurement of biomarkers of oxidative stress is subject to laboratory changes and differences between observers. It is widely known that, apart from changing one’s lifestyle, additional factors such as an optimal diet, healthy BMI, quitting smoking, and reducing the consumption of alcohol and caffeine may decrease oxidative DNA damage. Interventions aimed at overcoming oxidative stress in conditions such as miscarriages, pre-eclampsia, preterm birth, gestational diabetes, and intrauterine growth restriction are still being analyzed in various randomized studies

Key words: oxidative stress, pregnant women, complications of pregnancy, ROS, cancer

Introduction

Oxidative stress can be defined as a state of disrupted balance between reactive oxygen species and the mechanisms of detoxification and repair. Reactive oxygen species (ROS) are formed in every living cell during the physiological process of breathing, and a molecule of ROS contains an atom of oxygen with an unpaired electron [1, 2]. ROS react with the most important structures and cellular molecules and change the biological functions of these. Similarly, reactive nitrogen species (RNS) such as nitrous oxide (NO) or peroxynitrite (ONOO\(^{-}\)) have an impact on physiological cells or produce a plethora of toxic products. Excessive production of ROSs and/or RNSs leads to “oxidative” or “nitrogenous” stresses that play a vital role in many pathological processes typical of neoplastic diseases, neurodegenerative disorders, or illnesses with a viral, toxic, or inflammatory etiology [1, 3]. Pro-neoplastic activity of ROSs results mostly from DNA damage, proteins, and lipids, and modifying these molecules may increase the risk of mutation [4]. Factors which neutralize or stop the formation of free radicals also prevent mutagenesis, the transformation of phagocytic cells, and the destruction of DNA [1, 3].

Many types of DNA damage resulting from the activity of endogenous and exogenous factors are quickly detected. A complicated network of signal transduction pathways is later activated as a response to DNA damage [5]. The human ovum is relatively competent at repairing oxidative damage to DNA [6]. Unfortunately, however, information on the quality of DNA in human ova is scarce, most likely because of a lack of materials available for testing. By contrast, mature sperm is not usually capable of repairing damaged DNA [7]. During spermatogenesis, the maturing sperm gradually loses the ability to repair any DNA damage that may occur [8]. In a singular germinal cell exact replication of the genome is of the utmost importance [6]. The somatic cell as well as the germinal cell has three options of tackling DNA repairs. The first option is to activate apoptosis pathways. In this case, cell survivability will depend on the balance between pro- and anti-apoptotic factors in the ovum. The second option is damage tolerance, which may lead to mutation in the embryonic and somatic cells and, as a consequence, may cause further malformations and carcinogenesis in the next generation. The third option is to repair the damage [6]. Naturally, differences in the
ability to make repairs has an impact on the extent of oxidative damage to DNA as well as on the susceptibility of the individual to illnesses [9].

Repair mechanisms of oxidative damage to DNA

Human cells are equipped with three levels of protection. The first level of protection is the human MutT (hMTH1) homologue. This enzyme hydrolyzes 8-oxodGTP into 8-oxodGMP and prevents the use of an incorrect nucleoside triphosphate as a substrate for DNA polymerase. The second level of defense consists of special glycoside hydrolases that initiate repairs by means of base excision (BER). Lastly, there is the human MutY (hMYH) homologue which removes adenine that was incorrectly paired with 8-oxoGua [10-12].

Infertility and oxidative stress

It is assumed that in cases of infertility in couples, about 40% are caused by male factors related to sperm pathologies, including low sperm count, decreased motility, and incorrect morphology; the next 40% of cases are caused by female factors while the causes of the remaining 20% are unknown [13]. Chromosomal anomalies constitute the chief genetic factors responsible for infertility and recurrent miscarriage [14, 15].

Oxidative stress affects reproductive health, particularly in the pathogenesis of infertility [16]. It has been observed that among women who cannot be fertilized by the in vitro method, the extent of oxidative damage to DNA in the follicular fluid is higher than among fertilized women [17]. Furthermore, the extent of oxidative damage to DNA in the sperm during in vitro fertilization has been positively correlated with the retardation of implantation probability as well as increased frequency of miscarriage and diseases in the offspring, including childhood cancer [18].

Oxidative damage to DNA has long since been acknowledged as the principal etiological factor in damage to sperm DNA. Unlike a somatic cell, the sperm is very susceptible to damage as it has limited antioxidant and enzymatic protection [19]. ROS also causes gaps in the DNA strings of semen, and this results in oxidative modifications to nitrogenous bases such as 8-oxo-7,8-dihydroguanine (8-oxoGua).

Attempts to classify real idiopathic infertility have proven that the severity of oxidative damage to DNA in couples with a background of infertility or miscarriage is higher than in fertile couples with no history of miscarriage [20].

Oxidative damage to DNA and pregnancy

During a normal pregnancy, oxidative stress stimulates antioxidant mechanisms that are capable of reacting by way of enzyme activity and non-enzyme free radical deactivators. However, pregnancy is also a state in which this adaptation and balance may be easily disrupted [21]. Many recent studies have indicated that exposure to environmental contaminants during pregnancy is associated with damage to DNA in cord blood. Furthermore, exposure to contaminated air has many negative effects on human health. An evaluation of pregnant women living in polluted areas has clearly indicated higher numbers of MN frequency lymphocytes (for both the mother and the child) than among those living in an unpolluted environment [22-24].

Oxidative damage to DNA involves complications during early and later pregnancy

There is convincing evidence that a chronic inflammatory reaction combined with the presence of a local oxidizing environment may play a vital role in the etiology and development of complications during pregnancy [25]. Our modern sedentary lifestyle and exposure to toxins predispose the body to an increased amount of inflammation and oxidative stress, and these ultimately lead to higher oxidative damage to DNA. Increased damage to DNA may affect ova, sperm, and/or the development of the embryo, leading to infertility, miscarriage, and congenital defects. Apart from the damage caused to gametes, there is some probability that oxidative stress and system inflammation in the mother’s circulatory system may both be responsible for the basic complications—related anomalies. This is because genome instability may alter the phenotypes of cells and eventually decrease their proliferative potential, leading to complications related to abnormal placenta development. Furthermore, abnormal placenta development gives rise to hypoxia and reperfusion as a consequence of ischemia. As a result, the production of cytokines stimulated, generating dysfunctions in the endothelial cells that play an important role in the development of pregnancy complications [26].

In late pregnancy, damage to DNA (especially when it is caused by oxidative stress) is related to pre-eclampsia (PE), intrauterine growth restriction (IUGR), and the death of mothers in developing countries, and largely determines pregnancy—related susceptibility to diseases [27-29].

Increased oxidative stress in the placenta of women with PE and IUGR has been well documented. Nume-
rrous studies have supported the theory of insufficient blood supply to the placenta, modulating the mother’s metabolism, inflammation, and oxidative stress. This, in turn, leads to complications [28, 30, 31]. Oxidative stress has also been acknowledged as the main driving factor in placental apoptosis, releasing placental contaminants in to the mother’s bloodstream. It is considered to be a crucial pathogenic process in the development of PE [32].

A number of studies have discussed the influence of the mother’s oxidative stress on the later stages of pregnancy and resulting complications [33-35]. Recent studies have shown that the mother’s oxidative stress increases significantly in the third trimester and that the type of work has an impact on the oxidative stress levels of the mother as well as the placenta [36, 37]. A survey was conducted in which blood and urine samples were collected at various stages of the pregnancy between the 6th and the 8th weeks as well as after delivery among women who suffered no pregnancy complications. Additionally, 40 healthy women who were of childbearing age but not pregnant functioned as a control group. All markers of oxidative stress, including the urinary excretion of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), levels of 8-isoprostane in the blood plasma, total antioxidant capacity (TAC), glutathioneperoxidase of erythrocytes (GPX), and super oxided is mutation (SOD) have increased in the third trimester and most of them returned to non-pregnancy levels after the birth [36].

The same researchers conducted a study in which they measured the levels of various markers of oxidative stress in the blood plasma: total antioxidant capacity, 8-isoprostane, glutathione peroxidase of erythrocytes, the activity of superoxided is mutation in the urine: 8-oxodG among generally healthy, pregnant women between the 24th and 26th weeks of pregnancy. The same markers were then measured after birth and served as an evaluation of the relationship between the mother’s oxidative stress levels and the risk of complications during the next pregnancy (including pre-eclampsia, spontaneous preterm birth, and the newborn child being small for gestational age (SGA) or having a low birth weight (LBW) [37].

When compared to women who did not suffer complications during pregnancy, those with pre-eclampsia and those giving birth to small for gestational age (SGA) children were observed to have much higher levels of 8-isoprostane in the blood plasma. Meanwhile higher levels of 8-oxodG were found in the urine samples of women who delivered children of low birth weight, that is, below 2500 g. The above studies provide clear evidence that a heightened oxidative stress level in mothers in the second trimester involves pre-eclampsia, SGA, and LBW, suggesting that such stress plays an important role in the pathogenesis of pregnancy complications.

Oxidative stress during pregnancy and antioxidant supplementation

Some studies indicate that oxidative stress maybe crucial to the pathophysiology of pre-eclampsia only in some women and, because of that, there are no obvious benefits to using antioxidants to prevent such pathologies as have been observed in the whole populace of pregnant women from forming [38]. Studies concerning the effect of antioxidants other than vitamins C and E has decreasing the risk of complications during pregnancy, such as SGA and LBW, are worth pursuing further.

A few randomized clinical studies have failed to prove that supplementing with both vitamin C and E has a positive effect on the number of pre-eclampsia occurrences [39-42]. In fact, some studies have even proven that it can have a negative impact on the cells in the trophoblast placental functions [39, 43, 44]. Overall, the interpretations offered thus far on the ineffectiveness of anti-oxidative vitamins in decreasing the risk of pre-eclampsia have not been convincing.

Oxidative stress in cancer

Oxidative stress in a pregnant woman’s body can be compared to the state of oxidative stress found in the body of the cancer patient. Every cell in the body has a balance between the production of reactive oxygen species (ROS) that results in the formation of oxidative DNA damage and the removal of the so-called “background level” of these lesions [45] in other words, there is a definite balance between the formation of ROS that attack DNA in the course of metabolic processes and the removal of defects in these biomolecules by the specific enzymes that repair DNA. It is commonly known that DNA repair products (modified by oxidation of nitrogen bases and nucleosides that are cut in the repair process) are excreted in the urine as unchanged. High levels of urinary excretion of oxidative DNA damage indicate increased levels of oxidative stress in the organism as a whole. The work of several authors comparing the amount of markers of oxidative stress excreted in urine by patients diagnosed with cancer and by healthy controls shows that cancer patients excrete higher levels of these modifications. This significant increase in the number of analyzed markers of oxidative DNA damage may reflect the situation of oxidative shock that accompanies
cancer [46]. Cancer cells are characterized by consistently elevated levels of reactive oxygen species (ROS) and can therefore be particularly sensitive to increased oxidative stress [47].

It is also possible that the elevated levels of reactive oxygen species are associated with oncogenesis through oxidative damage to DNA. Cancer may increase the level of oxidative stress in the body and so affect the production of 8-oxoguanine. It has been shown that elevated levels of oxidative products in the urine DNA are associated with a greater stage of lung cancer [48]. Moreover, in patients with lung cancer these elevated levels have been linked with disease progression and oxidative stress [49]. In another work concerning patients with lung cancer who had either a partial or complete response to chemotherapy, 8-oxodG concentration in the urine was found to decrease, while those patients with disease progression showed an increase in concentration during treatment [50].

In their study, Roszkowski et al. [51] compared a large number of cancer patients (n = 222) and healthy volunteers (n = 134) with regard to the amount of 8-oxoGua and 8-oksydG secreted in their urine. It was found that from 50% to 80% of these markers were elevated in the cancer patients compared with healthy subjects. According to the authors, such a high level of this derivative in patients may not in fact be related solely to an increase in the number of cancer cells. The results suggest that oxidative stress in cancer patients (represented by the increased amount of these modifications in the urine) may be characteristic not only of the diseased tissue, but of other tissues and of the organism as a whole.

Conclusion

The referential values of ROS and NOS, their minimal and safe concentrations or physiologically beneficial concentrations are yet to be determined. Patients should be evaluated based on etiological factors and should undergo an individual analysis. This analysis should include their life style and diet. Additionally, an evaluation of their medical history based on the biological samples collected before giving birth, early and late miscarriage, and the health of the mother and the fetus, should be carried out.

Most of the published studies on oxidative stress are based on observation or are conducted in the form of case studies. They concentrate almost entirely on the relation between the DNA damage of the mother and the fetus or on the damage to the DNA of the sperm with relation to infertility. New studies should examine larger numbers of patients with similar resulting parameters in homogeneous populations. Damage to DNA should be evaluated using an identical technique, so that the results can be easily combined and compared. These studies may provide answers that could help predict pregnancy complications as well as possible interventions and preventive strategies.

The measurement of oxidative stress in vivo is perceived as controversial, as the sensitivity and specificity of various oxidative stress markers is unknown. The measurement of biomarkers of oxidative stress is subject to laboratory changes and to the differences between observers. It is widely known that, apart from changing one’s lifestyle, an optimal diet, healthy BMI, quitting smoking, and reducing the consumption of alcohol and caffeine may decrease the extent of oxidative damage to DNA.

Antioxidant supplementation-based treatment strategies aimed at reducing oxidative stress ought to be analyzed in randomized, controlled studies. Antioxidants may be recommended in cases where a specific etiology cannot be determined, for example, in idiopathic infertility, as there is no other proof based on the treatment of unexplained infertility and scientific reports strongly indicate the existence of oxidative stress in these cases.

Interventions to overcome oxidative stress in conditions such as miscarriages, pre-eclampsia, preterm birth, gestational diabetes, and intrauterine growth restriction are still being analyzed in various randomized studies.

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