

Oxidative stress and peripartum outcomes (Review)

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Abstract. Pregnancy, labor and childbirth are accompanied by excessive oxidative aggression. The excessive formation of free radicals [reactive oxygen species (ROS), reactive nitrogen species (RNS), chlorine reactive species (CRS)] causes cellular oxidative damage, which can be scavenged by enzymatic or non-enzymatic antioxidants in normal healthy pregnancy, physiological labor and delivery without any complications. An imbalance between the pro-oxidant and antioxidant factors may lead to oxidative stress, which contributes to the development of many diseases. This oxidative aggression can be a precursor for pathologies in the pregnant woman including eclampsia, miscarriage, preterm labor, and intrauterine growth retardation; in the offspring it may lead to bronchopulmonary dysplasia/chronic lung disease, necrotizing enterocolitis, retinopathy of prematurity, and periventricular leukomalacia. This review summarizes the studies conducted to identify the mechanisms of oxidative stress and the effect of cell membrane oxidation, the mechanisms that are behind oxidative stress-related diseases, and also those studies which have demonstrated the effect of antioxidants in preventing diseases or diminishing the effects of oxidative stress in the body, in obstetrics and neonatology.

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1. Introduction

Oxidative stress is defined as an imbalance between pro-oxidant and antioxidant factors. Free radicals are molecules with one or more unpaired electrons, extremely unstable and highly reactive. When produced in excess in the body, they become mediators of cell and tissue damage, resulting in a phenomenon called oxidative stress (1).

Reactive oxygen species (ROS) (such as the superoxide anion, hydrogen peroxide, hydroxyl radical, peroxy radical), reactive nitrogen species (RNS) [such as nitric oxide (NO), peroxynitrite, nitroxyl anion] and chlorine reactive species (CRS) (such as atomic chlorine, chlorine monoxide) have a general biological toxic effect, leading to direct peroxidation of membranes, proteins and structural enzymes, as well as nucleic acids. ROS, RNS, and CRS are molecules with free radicals or molecules without free radicals, but which can produce free radicals in certain conditions (reactive intermediates). Some free radicals, such as NO and the superoxide anion, are intentionally produced by the human body under certain conditions and at specific concentrations; they can serve as cell mediators with well-defined biological purposes (phagocytosis) (1).

Many low-molecular-weight enzymes and molecules have antioxidant capacity, protecting against these biochemical aggressors, as part of the antioxidant defense system by stabilizing free radicals (2). They are called free radical traps, but in biology and medicine are frequently referred to as antioxidants. These antioxidants can be grouped into two broad classes: endogenous (enzymatic, non-enzymatic) and exogenous (natural, synthetic) antioxidants, their mechanism of action depending on their nature (3). Most frequently, an electron transfer from the antioxidant to the free radical will stabilize the unpaired electron in the free radical, ending its highly reactive status. This transfer can take place in the form of a hydrogen atom or a covalent bond formation (4).

Total antioxidant capacity (TAC) is defined as a biological parameter, which sums up the antioxidant effects of low-molecular-weight enzymes and molecules with antioxidant properties in a living organism (5).

A panel of biomarkers of oxidative stress have been established for evaluation of the oxidative stress in pregnancy, in the fetus and the newborn (6), grouped according to their nature as: lipid peroxidation products (including

malondialdehyde, acrolein, isoprostanes), protein oxidation products (including protein carbonyl, tyrosine related groups), DNA oxidation products, stress response proteins, a novel biomarker (microRNAs) (6), and other biomarkers, such as enzymes (myeloperoxidase), thiols (glutathione) and metallo-thioneins (1). Furthermore, reduced and oxidized glutathione ratio (1) and non-protein-bound iron (6) have also been used as biomarkers in general analytical determinations (6).

2. Oxidative stress particularities in pregnancy, during labor and birth

The study of perinatal oxidative stress is considered a priority, due to the necessity to understand the pathophysiological mechanisms behind oxidative stress-related conditions in pregnancy and neonatal life (6).

In the evaluation of oxidative stress in pregnant women and the fetus, we must consider physiological aspects, i.e., the pregnancy as a condition, which exposes the pregnant woman to increased oxidative stress, and the placenta as the source of free oxygen radicals (7).

During delivery, the neonate is transferred from an intra-uterine hypoxic environment to an extrauterine normoxic one, which is believed to induce an elevated production of ROS and RNS (8).

Another aspect to be considered is the immaturity of the immune system in the fetus/newborn, concomitant with the marked exposure to the action of free radicals, the rapid increase in energy requirements after birth, the inefficient ability to achieve homeostasis, and immaturity of antioxidant capacity. These factors all predispose the newborn to significant oxidative stress (3). The inefficiency of enzymatic activity in the newborn has to be mentioned also, as it is an aspect that leads to increased oxidative stress in perinatal diseases (hypoxia, ischemia-reperfusion, activation of neutrophils and macrophages) (9).

Not only pregnancy, but labor and delivery all contribute to oxidative stress in different ways. Oxidative imbalance can pose a serious risk of complications, i.e. eclampsia, miscarriage, preterm labor, and intrauterine growth retardation (IUGR) (3,10-12).

Other authors have also reported accelerated ROS production in normal pregnancies due to increased metabolic needs (3). This increased metabolic rate allows adequate fetal growth and development, and is accompanied by enhanced oxidative stress in the placenta (13), but at the same time, it is counterbalanced by the elevated antioxidant levels (14).

Investigating oxidative stress markers at the time of birth, Arguelle *et al* found a positive correlation between high maternal levels of oxidative stress corresponding to even higher oxidative stress levels in newborn umbilical cord blood (15). According to Gitto *et al* hypoxic periods and oxidative stress periods may alternate during labor and birth, and fetal plasma has a low concentration of antioxidants to resist those oxidative damages (2). This could explain the higher oxidative stress in the neonate compared to the mother.

By investigating the type of delivery, many authors have concluded that there is the same degree of fetal oxidative stress via vaginal delivery or Caesarean section (16,17). Other studies comparing vaginal delivery with Caesarean section have

demonstrated that the type of delivery influences the oxidative status of the term newborn. These studies have found reduced antioxidant capacity in preterm and term infants (18-20).

According to Chiba *et al* increased production of oxidative stress markers is present in women with prolonged vaginal delivery and emergency Caesarean section (21).

During labor, an overwhelming oxidative imbalance can occur, which can result in ischemic reperfusion injury produced by powerful uterine contractions, affecting the neonate and predisposing them to oxidative stress (3).

Karacor *et al* reported significantly higher total antioxidant status (TAS) and total oxidative status (TOS) levels in pregnant women undergoing oxytocin-induced labor compared to a control group (spontaneous births). It was concluded that oxytocin used to induce childbirth is an additional stress and increases the intensity of oxidative stress and thus, antioxidant processes will be more pronounced: NO, catalase, glutathione peroxidase and glutathione were increased due to response to oxidative stress (7). NO is a biologically important molecule which can serve as an antioxidant and also as a free radical source through peroxynitrite formation; the effect depends mostly on its concentration: low levels of NO protect the organs from ischemic damage (22).

Vural *et al* report that oxidative stress was increased in recurrent or habitual abortion, as the antioxidant mechanisms were insufficient to compensate the increased oxidative stress; thus, oxidative stress may be involved in the etiology of abortion (23).

Some reports indicate transplacental transfer of antioxidants at the end of gestation (18).

The effectiveness of antioxidant mechanisms in neonates largely depend on the functionality of the maternal antioxidant system. The efficiency of antioxidant mechanisms can be influenced by maternal factors, i.e. age, parity, nutritional status, or environmental and genetic factors, which can cause an imbalance in the newborn in addition to their immaturity (3).

In uncomplicated pregnancies, there is a balance between the antioxidant system and reactive intermediates, but this balance can be disrupted due to complications in the pregnancy or labor with poor outcomes (3,24).

Comparing oxidative stress levels in early vs. late cord clamping births, Diaz-Castro *et al* concluded that there is another possible oxidative stress factor in late cord clamping due to an increase in the concentration of free Fe²⁺ ions, especially in preterms with a lower level of iron carriers. Fe²⁺ is not a free radical, but it can induce the decomposition of the relatively stable hydrogen peroxide molecule, through an electron donating process, to one of the most dangerous free radicals that can be encountered in the biological environment: the hydroxyl free radical. In addition, the TAS was found to be higher in the late-clamped group, which suggests a protective effect of late cord clamping. The oxidative damage caused by ROS was found to be partly neutralized by catalase (CAT) and superoxide dismutase (SOD), sustained by the observed greater enzyme activity in the late-clamped group (25). In addition, prenatal steroid administration significantly intensified enzyme activity according to Wilinska *et al* and Vento *et al* (26,27). Decreased CAT activity was reported in pregnant women undergoing instrumental delivery due to the threat of eclampsia (26). The activity of both enzymes is

probably important because superoxide dismutase converts superoxide anion to hydrogen peroxide, a more stable molecule but with a potential to generate under certain conditions powerful oxidative damage, especially through the Fenton reaction. In a second step CAT and other enzymatic systems reduce hydrogen peroxide to water and molecular oxygen (1).

There are several studies which suggest that there are some benefits of delayed cord clamping; i.e. improvement in cardiopulmonary adaptation, lower RDS frequency, reduced incidence of intraventricular hemorrhage, lower anemia rate in infancy and longer period of breastfeeding (28-30).

A non-invasive determination method for the oxidative stress biomarkers is from saliva with the same accuracy and specificity as from plasma samples. Studying the oxidative stress biomarkers in saliva and blood samples of mothers and their newborns delivered with or without combined analgesia, Shobeiri *et al* did not find any statistically significant difference between the two groups (31); according to their findings, combined analgesia is not a contributing factor to oxidative stress.

In gestational diabetes, due to the metabolic disturbances during pregnancy (mitochondrial superoxide overproduction is due to elevated glucose level and endothelial cells are the main targets of the induced oxidative stress), higher levels of oxidative stress are observed. Neonates born from diabetic mothers have elevated oxidative stress parameters and decreased antioxidant capacity, compared to newborns from healthy physiological pregnancies (26).

3. Oxidative stress-related conditions in the newborn

There are several conditions involved in 'oxygen radical diseases in neonatology'. This category has been postulated by Saugstad and includes bronchopulmonary dysplasia/chronic lung disease, retinopathy of prematurity and necrotizing enterocolitis (32). Yet, later it was clarified that periventricular leukomalacia (33), ductus arteriosus and pulmonary circulation are affected by free radicals as well (34-36).

Demonstrating the effect of antioxidants in disease prevention or in diminishing the effects of oxidative damage, and the scientific curiosity to understand the mechanisms of action of injuries caused by free radicals, have led to widespread research in obstetrics and neonatology. Several experimental and clinical studies have warned that the use of high concentrations of O₂ in neonatal resuscitation will not confer benefits in reduced hypoxic-ischemic encephalopathy and mortality, but the oxidative stress will be more elevated compared to ambient oxygen, and the guidelines recommend the use of an oxygen blender and pulse oximetry during resuscitation of the preterm, and the use of oxygen concentrations between room air and 100%, adjusted according to the infant's needs to reach a saturation of 95%. According to those meta-analyses and multicentric trials (37-39), neonatal mortality was reduced by 30-40% when resuscitation was carried out with 21% oxygen instead of 100% (2).

One of the possible side effects of elevated O₂ exposure is the increased likelihood of leukemia, as oxygen derivatives can damage DNA, and sometimes, through DNA damage, they can lead to formation of cancer cells (40).

Because neonates are at a very early stage of lung development with immaturity of the cells that are important for

maturation of the airways, an inadequate antioxidant response to increased ambient oxygen and poor surfactant production have been observed (2).

ROS/RNS induce changes in the pulmonary endothelial cell structure, which leads to focal hypertrophy and altered metabolic activity. This plays a role in the pathogenesis of inflammatory pulmonary diseases, i.e. respiratory distress (RDS) of the newborn (41). Gitto *et al* concluded that RDS is associated with elevated ROS/RNS generation, and this leads to increased oxidative damage to the lung (2).

In premature newborns with poorly developed antioxidant defense mechanisms, even a lower concentration of supplemental oxygen may generate oxidative stress and secondary to that, lung injury. In addition, inflammatory cell accumulation and activation may generate oxidative stress, which can lead to chronic lung disease (CLD) (42). In contribution to the investigations of the mechanisms for developing CLD, Ramsay *et al* demonstrated that premature infants who developed CLD have oxidized specific proteins more frequently, than those without CLD (43). In their review, Gitto *et al* concluded that identification of these specific proteins which are more frequently oxidized in preterms who develop CLD, can lead to establishment of specific mechanisms for development of CLD (2).

As earlier studies have suggested, the main source of free radicals in the lung is phagocyte activation (44,45). Bancalari and Gonzales and Speer and Groneck described in their studies that those infants who develop CLD have increased pro-inflammatory cytokine levels in their airway samples (46,47). Oxidative stress can cause chronic inflammation, by activation of macrophages, which produce pro-inflammatory cytokines, such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α . Other studies suggest that the presence of IL-10 as an anti-inflammatory cytokine in the lower airway prevents the development of CLD in preterm infants (48).

There are sufficient published data that suggest that ventilation can lead to elevated cytokine levels in neonates, and the most effective strategy is the use of nasopharyngeal continuous positive airway pressure and the avoidance of mechanical ventilation (2). Upon comparing high frequency oscillatory ventilation (HFOV) to conventional mechanical ventilation (CMV), the Cochrane Database concluded that there is no clear evidence on better outcome, when HFOV was used as elective initial ventilation strategy over CMV (2).

CLD is one of the most important factors in the mortality and morbidity of a preterm infant; especially in case of extremely low birth weight (VLBW) infants. The exposure of these immature lungs to prolonged periods of high O₂ concentration is considered to be an important factor in the development of CLD. Saugstad concluded that the effect of free radicals on endothelial and epithelial cell membranes induces pulmonary edema and triggers the activation and accumulation of inflammatory cells (49).

Chitra *et al* found higher MDA plasma levels in neonate than in the maternal plasma. Uterine contractions produce a fluctuation in uterine blood flow (ischemia followed by reperfusion), a process known to generate free radicals. In uncomplicated births, oxidative stress is more effectively counterbalanced by the body's antioxidant power, compared to complicated births (3).

4. Circulating biomarkers and oxidative stress evaluation

The evaluation of oxidative stress based on the level of peroxidation is conducted by determining malondialdehyde (MDA) levels. MDA is a product of the lipid peroxidation process along with other aldehydes and is frequently and preferentially used as a biochemical marker to assess the intensity of this process (7). In a review by Gitto *et al* elevated MDA concentrations were described in distressed fetuses delivered by emergency Caesarean section compared to non-distressed newborns delivered by elective Caesarean section (2). Lurie *et al* described that as the result of increased distress, MDA levels and glutathione oxidase activity of amniotic fluid and cord blood were elevated in case of fetuses born via emergency caesarian section, and that gender or type of anesthesia had no influence on the concentration of these biomarkers (50).

Karacor *et al* concluded in their study that MDA levels were significantly higher in pregnant women who underwent oxytocin-induced labor compared to the control group, which implies that the administration of oxytocin leads to maternal and fetal stress, which is why the concentration of MDA is increased (7). Another study by Schneid-Kofman *et al* also describes higher concentrations of MDA in pregnant women with induced labor, but with low level of the antioxidant glutathione (51). Glutathione is important in stopping the lipid peroxidation process, in which the starting free radical is regenerated and available to restart another lipid peroxidation process, by reacting with the lipid peroxide intermediates and preventing the perpetuation of the process. According to Rogers *et al* the increase in MDA levels in the umbilical cord blood may suggest a state of hypoxia and may also be caused by perinatal stress (52).

According to Chitra *et al* MDA levels in maternal and fetal plasma were significantly different. Based on this difference, birth predisposes the fetus to more intense oxidative stress compared to pregnant women, but the oxidative status of both (mother and fetus) is significantly altered (3). In a study of the oxidative status of low-birth-weight infants (LBW), Negi *et al* reported that MDA plasma concentrations were higher in LBW infants compared to a normal birth-weight control group, and at the same time they have found decreased levels of TAS, and vitamins A, E and C (dietary antioxidants) (53).

According to Wilinska *et al* plasma MDA levels were elevated in full-term infants and their mothers, but MDA levels in breast milk decreased in the first days after birth, probably due to the reduced metabolic need. It was also observed that breast milk has high antioxidant content, at least in the first couple of days after birth, which is beneficial to the newborn (26).

According to Howlander *et al* maternal and fetal oxidative stress in cases of preeclampsia was characterized by increased serum MDA levels in both mother and fetus, compared to a healthy control group. At the same time, an increase in ROS and decrease in TOS and vitamin C levels were observed in the fetal circulation, and protein carbonyl levels were significantly higher compared to the control group (54).

TAS (also mentioned by some authors as total antioxidative capacity) and TOS (or total oxidative capacity) were studied by multiple authors. According to Alberti-Fidanza *et al* the diet of pregnant women significantly influenced the total antioxidant capacity, which was much higher in mothers who had a diet rich

in vitamins (55). However, this should also be correlated with the meta-analysis of Bjelakovic *et al* who reported that high consumption of antioxidant supplements (vitamin A, E) may be associated with increased mortality, and that the potential role of vitamin C in decreasing life expectancy of well-nourished adults, needs further investigations. Antioxidant source should be dietary and not from supplements, the authors suggest (56).

According to Özalkaya *et al* TOS is much higher in cases of premature rupture of membranes and TAS is lower in cases of premature rupture of membranes and fetal inflammatory response syndrome. Also, they suggest that oxidative stress is responsible for the premature ageing of the fetal membranes of infants born before 34 weeks of gestation (57). This thesis is also supported by a number of studies carried out by Menon and Richardson (58) and Ilhan *et al* (59). According to Wilinska *et al* TAS has a declining trend in newborns during the first days of life (26).

The study of Arguelles *et al* concluded that based on TAS, under normal conditions, the level of maternal and fetal oxidative stress displays no significant differences, but an excess of maternal oxidative stress (caused by smoking, inappropriate lifestyle, diabetes mellitus, metabolic diseases) causes even more severe fetal oxidative stress at birth; therefore, monitoring and control of maternal oxidative stress during pregnancy is important (15). According to Howlander *et al* TAS was significantly lower in pregnant women with preeclampsia, which demonstrates that preeclampsia is an important perinatal pathology, which causes extra stress to both the maternal and fetal organism (54).

In the study by Seligman *et al* NO levels were lower in preeclamptic women than in healthy pregnant ones (60), in accordance with the findings of Conrad *et al* who described lower levels of NO and cGMP in preeclamptic patients (61).

In their study Karacor *et al* found no statistically significant difference in NO levels between the oxytocin-induced labor group and control group, thus they suggested that antioxidant mechanisms were functioning well in both groups and stress only is not enough to cause alteration in NO levels (7).

5. Conclusions

Upon the attempt to summarize the results of studies performed on pregnant women and newborns, we conclude that all these studies underline the need to understand the mechanisms of action of free radical formation and their action on the maternal and fetal organism, in order to identify strategies to reduce the level of oxidative stress, and minimize the harmful effects of this process on both mother and newborn.

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Authors' contributions

ZSS performed analysis of the current published data. ZSS and MC drafted the original manuscript. EF, ENN and LD performed critical revision of the manuscript. BS provided expertise in the field of obstetrics. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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