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The role of methemoglobinemia in early and late complicated pregnancy

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Summary The objective of this review was to direct attention about methemoglobin as a biomarker which has an important role in the detection of adverse effects of the oxidative stress, misbalanced production of ROS, RNS and RSS. According to our hypothesis, a pregnant woman continuously inhaling environmental toxics as fuel burning products, will traverse three, not two from current thought, distinct stages. The main difference among present three-stage hypothesis and other hypotheses is the assertion that, in the pathogenesis of early and late complicated pregnancy, methemoglobin takes on an important role. Secondly, we also observed the utero-placental changes as ''locus manifesting minoris resistentiae'' in complicated pregnancy are not the causes but a consequence of increased systemic oxidative stress. Methemoglobin and hemolysis both occur as a result of oxidative stress, but the prevalent difference between them is that methemoglobin is a reversible phenomenon (oxidant–antioxidant balance) whereas hemolysis, which occurs as a result of oxidative stress on the erythrocyte membrane, is an irreversible event. Methemoglobinemia can additionally exacerbate an existing anemia, stimulating hypoxia that may be dangerous for both mother and fetus. Own prospective study of methemoglobin in pregnancy, revealed a significant rise in the level of methemoglobin >1.5 g/L ($r = 0.72$, $p < 0.01$) in the exposure period, which can be explained on the basis of an oxidant–antioxidant imbalance, resulting in methemoglobinemia. Methemoglobinemia and stillbirth recorded throughout exposure period are significantly higher than those recorded in the control period ($p = 0.0205$), and the frequencies of reproductive loss were significantly lower in the *control* than in the *exposure* period ($p < 0.05$). Results suggest that methemoglobin as individual indicator of oxidative stress is an early marker of the identification of women with a pregnancy risk. It has the advantage of being applicable some time before ultrasonic examination becomes feasible. Further support for this assumption will require further investigations that may lead to the supposition that increasing level of methemoglobin is related to environmental toxicities complicated pregnancy and IUGR, preeclampsia, and a high percentage of perinatal mortality and morbidity.

Introduction

The main difference among present three-stage hypothesis and other hypotheses is the assertion that, in the pathogenesis of preeclampsia, methemoglobin takes on an important role. This opinion result using edemiologically a very important envi-

Abbreviations: TE, thermoelectric; TSP, total suspended particulate; LBW, low birth weight; MetHb, methemoglobin; IUGR, intrauterine growth restriction; ROS, reactive oxygen species; RNS, reactive nitrogen species; RSS, reactive sulfur species.

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ronmental factors as *Continuous* inhalation of oxidants, nitrogen oxides, sulfur dioxide and their metabolites over longer periods, causes maternal vascular endothelial dysfunction from the early pregnancy to the end stage. Also of major importance are factors, such as *the Intensity* of exposure, the *Accumulation* of oxidants causing oxidant–antioxidant imbalance and the *Synergism* of nitrogen oxides–sulfur dioxides metabolites.

Recent intensive studies indicate oxidative stress as the genesis of endothelial dysfunction in atherosclerosis, and propose that oxidative stress can lead to the pregnancy endothelial dysfunction linking the two stages; failed vascular remodeling of the vessels that supply the placental bed (stage 1) and the multisystemic maternal syndrome of preeclampsia (stage 2) [1,2].

The facts that the IUGR is a result of reduced perfusion, and that many women with growth restricted infants do not have preeclampsia, and that a small percentage of preeclamptic women have large fetuses, confuse the role of oxidative stress in the pathogenesis of preeclampsia. Why do reduced placental perfusion and abnormal implantation occur without the maternal syndrome; how does this translate into maternal disease in some but not all women; and what is the connection between these two stages are the topics of intensive study.

The arguments presented by Jenkins et al. elucidated that those pregnancies which completed the term successfully were associated with increased levels of antioxidants early in the first trimester, but the first trimester miscarriage was associated with significantly reduced levels of superoxide dismutase, which appear to be associated with increased oxidative stress [3].

Nitric oxide is a potent vasodilator produced by the endothelial cells. Burning of wood or kerosene, gas stoves, coal burning power plants, smoke of heavy motor vehicle and cigarette smoke, results in the emission of nitrogen oxide and sulfur dioxide, which can be toxic on excessive inhalation. Potential metabolic toxicities are related to toxic effect of nitric oxide and its metabolites such as nitrogen dioxide as strong hemoglobin oxidants. It is known that superoxide reacts with nitric oxide to produce peroxynitrite, a strong oxidant which readily catalyzes membrane lipid peroxidation [4]. Methemoglobin and hemolysis both occur as a result of oxidative stress, but the prevalent difference between them is that methemoglobin is a reversible phenomenon whereas hemolysis, which occurs as a result of oxidative stress on the erythrocyte membrane, is an irreversible event. Balla et al. demonstrate that reduced ferrohemoglobin, while relatively innocuous to cultured endothelial cells, when oxidized to ferrihemoglobin (methemoglobin), greatly amplifies oxidant (H_2O_2)-mediated endothelial-cell injury [5].

Recently, Liu and Spolarics found that methemoglobin is a potent activator of endothelium cells and chemokine and cytokine production, and the endothelial cells are direct targets of free hemoglobin or its oxidative derivatives including methemoglobin and hemin [6]. The physiological level of methemoglobin is 1% and it may increase when erythrocytes are affected by a variety of genetic, dietary, idiopathic, toxic, xenobiotic pharmaceutical and environmental compounds. Several intracellular mechanisms exist to maintain a low level of methemoglobin under normal conditions [7,8].

Not only the effects of hemoglobin oxidation impact the rise in methemoglobin concentration, but even the inhibition or the consumption of enzyme and non-enzyme antioxidants can cause toxic methemoglobinemia [9,10].

Preeclampsia: a three-stage disorder

According to our hypothesis, a pregnant woman continuously inhaling nitrogen oxides and sulfur dioxide as fuel burning products, will traverse three, not two from current thought, distinct stages.

First stage (blood circulation stage)

The inhalation of a continuous, but not extremely high level of nitrogen oxides (nitrogen dioxide and nitric oxide) from the time of preconception enters the mother's blood circulation directly through the alveolar-capillary membrane, transforming the hemoglobin into its pathological reversible form methemoglobin, including altered vascular reactivity, initiate oxidative damage and endothelial cell dysfunction. The formation of methemoglobin leads to the destruction of erythrocytes and farther consequences [11].

Second stage (deciduo-placentation stage)

Continued chronic exposure (>24 h a day) to inhaled oxidants prolongs systemic vascular endothelial dysfunction and the spiral arteries of the decidua and myometrium, a reproductive ''locus minoris resistentiae'' susceptible organ, leading to a failure to establish an adequate uteroplacental blood flow. This condition is thought to give rise to relatively hypoxic trophoblast tissue, and may promote an exaggerated state of oxidative stress in