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OXIDATIVE STRESS IN THE PATHOGENESIS OF OBSTETRIC AND PERINATAL COMPLICATIONS

Abstract. Oxidative and nitrosative stress are recognized as universal pathogenic mechanisms that play a pivotal role in the onset and progression of obstetric and perinatal complications. This review summarizes current evidence on the impact of oxidative stress on pregnancy, placental development, and the formation of various complications, with a particular focus on preeclampsia. Literature indicates that an imbalance between pro-oxidant factors and the antioxidant defense system leads to damage to nucleic acids, lipids, and proteins, activation of apoptosis and inflammatory responses, and impairment of endothelial function and microcirculation. These processes underlie abnormal placentation, fetal hypoxia, growth restriction, and increase the risk of preterm birth, miscarriage, low birth weight, and congenital anomalies.

Special attention is given to preeclampsia as a clinical model of oxidative–nitrosative injury. Excessive production of reactive oxygen and nitrogen species combined with reduced nitric oxide bioavailability provokes platelet aggregation, placental ischemia-reperfusion injury, and intravascular coagulopathy, directly impairing uteroplacental blood flow. Evidence indicates that manifestations of

oxidative stress may appear as early as the first half of gestation and persist after delivery, predisposing to neonatal diseases linked to oxidative damage, particularly in preterm infants (bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, periventricular leukomalacia, and others).

Recurrent pregnancy loss is highlighted as a condition reflecting chronic oxidative imbalance: affected women show reduced adaptive capacity and down-regulation of antioxidant defenses. Preterm birth, which is increasing worldwide, is associated with elevated oxidative stress markers in maternal serum during threatened preterm labor. A promising approach involves assessing oxidative-stress and antioxidant parameters in umbilical cord blood of preterm neonates as a tool for predicting specific neonatal pathologies.

Despite the large body of research, there are still no unified approaches for quantitative assessment of oxidative stress or for selecting reliable prognostic biomarkers for routine clinical practice. Future research priorities include the development and clinical implementation of standardized biomarker panels to identify pregnant women at high risk of preeclampsia and other complications, deeper investigation of genetic and epigenetic regulators of redox homeostasis, and the creation of novel antioxidant therapeutic strategies aimed at the prevention and treatment of gestational disorders.

Keywords: oxidative stress; nitrosative stress; pregnancy; preeclampsia; recurrent pregnancy loss; preterm birth; fetoplacental insufficiency; biomarkers; umbilical cord blood; antioxidant defense.

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ОКСИДАТИВНИЙ СТРЕС В ПАТОГЕНЕЗІ АКУШЕРСЬКИХ ТА ПЕРИНАТАЛЬНИХ УСКЛАДНЕНЬ

Анотація. Оксидативний та нітрозативний стрес нині розглядаються як універсальні патогенетичні механізми, що відіграють провідну роль у виникненні та прогресуванні акушерських і перинатальних ускладнень. Метою цієї роботи є узагальнення сучасних даних щодо впливу оксидативного стресу на перебіг вагітності, розвиток плаценти й формування різноманітних ускладнень, зокрема прееклампсії. У статті наведено огляд літератури, який демонструє, що дисбаланс між прооксидантними факторами та системою антиоксидантного захисту призводить до пошкодження нуклеїнових кислот, ліпідів та білків, активації апоптозу та запальних реакцій, порушення ендотеліальної функції й мікроциркуляції. Ці процеси спричиняють патологію плацентації, гіпоксію, затримку росту плода, підвищують ризик передчасних пологів, викиднів, низької маси тіла новонароджених і розвитку вроджених вад.

Особливу увагу приділено прееклампсії як клінічній моделі оксидативно-нітрозативного ушкодження. Підкреслено, що надмірне утворення активних форм кисню та азоту на тлі зниження біодоступності оксиду азоту провокує агрегацію тромбоцитів, ішемічно-реперфузійне ураження плаценти та внутрішньосудинну коагулопатію, що безпосередньо впливає на матково-плацентарний кровоплин. Встановлено, що прояви оксидативного стресу можуть з’являтися вже у першій половині гестації й зберігатися після пологів, що створює умови для формування у новонароджених захворювань, пов’язаних з оксидативним ушкодженням, особливо у недоношених дітей (бронхолегенева дисплазія, ретинопатія, некротичний ентероколіт, перивентрикулярна лейкомаляція та інші).

Окремо розглянуто звичне невиношування як стан, що відображає тривалий оксидативний дисбаланс: у пацієнток фіксують зниження резервно-адаптаційних можливостей та пригнічення антиоксидантних систем. Для передчасних пологів відзначено глобальну тенденцію до зростання частоти та асоціацію з підвищенням маркерів оксидативного стресу у сироватці крові на тлі загрози передчасних пологів. Перспективним підходом є оцінювання маркерів оксидативного стресу та антиоксидантних компонентів у пуповинній крові недоношених новонароджених як інструменту прогнозування ризиків окремих неонатальних патологій.

Незважаючи на значний обсяг наукових робіт, нині відсутні уніфіковані підходи до кількісної оцінки рівня оксидативного стресу та відбору достовірних прогностичних маркерів для рутинної клінічної практики. Перспективними напрямами подальших досліджень є розроблення та впровадження стандартизованих біомаркерів, що дозволять своєчасно ідентифікувати вагітних із високим ризиком прееклампсії та інших ускладнень, поглиблене вивчення генетичних і епігенетичних механізмів регуляції окисно-відновного гомеостазу, а також

створення нових антиоксидантних терапевтичних стратегій, спрямованих на профілактику й лікування гестаційних порушень.

Ключові слова: оксидативний стрес; нітрозативний стрес; вагітність; прееклампсія; звичне невиношування; передчасні пологи; фетоплацентарна недостатність; біомаркери; пуповинна кров; антиоксидантний захист.

Problem statement. Oxidative and nitrosative stress are now widely acknowledged as fundamental pathogenic mechanisms in a broad spectrum of human diseases. Their influence extends well beyond classical cardiovascular or metabolic disorders, exerting a profound and multifaceted impact on female reproductive health, the physiological course of pregnancy, and perinatal outcomes at both the maternal and neonatal levels [1,2]. Free radicals (FR) – highly reactive molecular species with unpaired electrons – are capable of damaging virtually all classes of biological molecules. By modifying lipids, proteins, and nucleic acids, FR disturb the normal cellular redox balance and trigger a cascade of biochemical events that compromise tissue integrity and function [3]. Such processes are particularly critical in pregnancy, where the delicate equilibrium between oxidative reactions and antioxidant defenses determines the success of implantation, placentation, and fetal development.

Analysis of recent research and publications. Under normal physiological conditions, the healthy organism maintains a dynamic equilibrium between pro-oxidants and antioxidants through an intricate defense network that includes enzymatic and non-enzymatic mechanisms. This system provides continuous protection against reactive oxygen species (ROS) and other free radicals, preventing excessive accumulation of oxidative products and maintaining redox homeostasis [4]. When this finely tuned balance is disrupted – whether by increased FR formation, diminished antioxidant capacity, or a combination of both – oxidative stress (OS) develops. OS in turn leads to structural and functional damage to nucleic acids, lipids, and proteins [2]. Numerous studies demonstrate that excessive and uncontrolled ROS production during pregnancy has far-reaching consequences: it adversely affects maternal health, impairs embryonic and fetal development, and contributes to a variety of complications including implantation disorders, spontaneous miscarriage, preterm birth, low birth weight, and congenital malformations. Moreover, heightened OS weakens maternal immune competence and interferes with the rapid pulmonary adaptation required for neonatal survival immediately after delivery [5].

The aim of the article. To summarize current evidence on the role of oxidative and nitrosative stress in the pathogenesis of obstetric and perinatal complications, with particular attention to preeclampsia.

Presentation of the main material. Pregnancy represents a remarkable state of continuous maternal adaptation to profound anatomical, physiological, and metabolic changes, many of which are driven by the high metabolic demands of the developing feto-placental unit [6]. Numerous anatomical, physiological, and metabolic adjustments occur during gestation [5]. The placenta, as the interface between mother

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and fetus, exhibits intense mitochondrial activity and produces significant amounts of ROS even under normal conditions. In healthy pregnancies, this rise in ROS generation is counterbalanced by a parallel increase in antioxidant defenses, ensuring that oxidative reactions remain within physiological limits. When this compensatory mechanism is inadequate, the balance tips toward oxidative predominance, resulting in sustained OS [7]. Consequently, pregnancy is often described as a state of heightened susceptibility to oxidative stress, primarily due to the placenta's elevated oxygen consumption and mitochondrial energy requirements [8]. Impaired antioxidant activity during critical stages of placentation can accelerate lipid peroxidation, damage vascular endothelium, and disrupt normal angiogenesis. At the same time, an up-regulation of certain antioxidant enzymes may act as a partial, though frequently insufficient, compensatory response [9,6]. These molecular events highlight the delicate interplay between oxidant production and antioxidant protection throughout gestation.

Accumulating evidence indicates that OS contributes to pregnancy loss through multiple, often overlapping mechanisms. These include disruption of uteroplacental blood flow, induction of apoptosis in fetal and placental cells, activation of inflammatory pathways, and dysregulation of immune responses [10]. Importantly, biochemical markers of OS can be detected as early as the first trimester and may persist well beyond delivery, influencing both prenatal and postnatal health [11]. After birth, additional stressors – such as hypoxia, ischemia, and rapid hemodynamic changes – can further exacerbate oxidative injury. Neonates are particularly vulnerable because their endogenous antioxidant systems are immature. Preterm infants are at even greater risk, facing a pronounced imbalance between oxidant generation and antioxidant protection that gives rise to a spectrum of conditions collectively known as free radical-related diseases of prematurity. These include bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, renal injury, eryptosis, respiratory distress syndrome, and persistent ductus arteriosus, among others [12-14].

Among the many pregnancy complications associated with OS, preeclampsia (PE) occupies a special and extensively investigated position. PE is characterized by reduced nitric oxide (NO) bioavailability, placental ischemia–reperfusion injury, and tissue damage caused by excessive levels of ROS and reactive nitrogen species (RNS). These reactive molecules promote platelet adhesion and aggregation, intravascular coagulopathy, placental infarction, and impaired uteroplacental perfusion, ultimately leading to fetal hypoxia and growth restriction [15]. PE remains one of the most prevalent obstetric syndromes and continues to be a leading cause of maternal and perinatal morbidity and mortality worldwide [16]. Numerous experimental and clinical studies confirm the pivotal role of OS in the pathogenesis of PE [17-23]. Oxidative agents generated during placental ischemia-reperfusion can overwhelm endogenous antioxidant defenses, and this imbalance is now considered a defining feature of the disorder [24]. Notably, investigations reveal that women who subsequently develop PE often exhibit biochemical evidence of OS as early as 16-20 weeks of gestation, a period

critical for normal placental development. Such early oxidative disturbances may not only impair placentation but also program long-term non-communicable diseases in the offspring [25]. Given these observations, there is a compelling need to identify and validate novel biomarkers capable of detecting pregnancies at high risk for PE in the earliest stages. Early detection would facilitate targeted prophylaxis and the development of innovative therapeutic strategies aimed at modulating redox homeostasis [26]. Yet, despite decades of research, no universally accepted parameters or standardized assays currently exist for the routine clinical assessment of OS in the reproductive system or pregnancy-related conditions [27].

Interest in the relationship between OS and recurrent pregnancy loss has also intensified. Recent investigations provide deeper insights into key pathogenic mechanisms and reveal potential therapeutic targets [28,29]. Women with recurrent miscarriage frequently demonstrate diminished adaptive capacity and down-regulation of antioxidant defenses, creating a biochemical milieu conducive to lipid peroxidation and sustained oxidative damage [30].

Preterm birth (PTB) continues to be a major obstetric challenge and remains one of the leading causes of neonatal morbidity and mortality. Despite advances in perinatal care and active implementation of preventive measures, global PTB rates have shown little decline and, in some regions, continue to rise [31]. Elevated maternal OS is strongly associated with an increased risk of PTB. Several clinical studies evaluating serum OS biomarkers in women with threatened preterm labor have documented significantly higher concentrations of these markers, although their specificity for predicting individual outcomes remains limited [32,33]. In contrast, assessment of oxidative and antioxidant parameters in umbilical cord blood of preterm neonates shows promise as a tool for identifying infants at risk of particular complications. The consequences of oxidative injury are not confined to the immediate perinatal period; they extend into infancy and childhood, contributing to both short- and long-term morbidity [34].

Taken together, these data provide convincing evidence that OS impairs reproductive function and contributes to the pathophysiology of a wide range of complications, including infertility, recurrent miscarriage, PE, fetal growth restriction, and PTB [35]. Excessive ROS production disrupts critical developmental processes, elevates the risk of complicated gestation, and may exert lasting effects on offspring health [36]. As a result, the study of oxidative mechanisms in reproduction has become a rapidly expanding and highly promising field of biomedical research.

Conclusions. Oxidative and nitrosative stress constitute a central, unifying mechanism in the pathogenesis of numerous obstetric and perinatal complications, with preeclampsia serving as a particularly illustrative model. The excessive generation of reactive oxygen and nitrogen species, combined with depletion or functional exhaustion of antioxidant defenses, precipitates cellular injury, abnormal placentation, chronic hypoxia, and fetal growth restriction. Evidence indicates that biochemical signs of oxidative stress may emerge during the earliest weeks of gestation and can persist

long after delivery, contributing to neonatal disorders associated with oxidative damage – especially in premature infants.

Despite the considerable body of experimental and clinical research, there are still no standardized, clinically validated biomarkers that reliably quantify oxidative stress or accurately predict obstetric complications. Future investigations should therefore prioritize the development and large-scale validation of predictive biomarker panels, the exploration of genetic and epigenetic regulators of redox homeostasis, and the design of effective antioxidant interventions. Such strategies hold the potential not only to prevent preeclampsia but also to reduce the global burden of pregnancy-related complications and improve long-term outcomes for both mothers and children.

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