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THE ROLE OF HORMONAL AND NON-HORMONAL MARKERS IN ASSESSING PERINATAL STRESS AND ITS CLINICAL IMPLICATIONS

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ABSTRACT

Background: Prenatal and perinatal stress activates the maternal and fetal HPA axis, releasing biomarkers that can cross the placenta. In high concentrations, these substances may lead to congenital malformations, preterm labor, or intrauterine growth restriction (IUGR). Despite their potential, endogenous biomarkers are not yet part of standard gynecological diagnostics.

Aim: This paper analyzes recent reports on hormonal and non-hormonal perinatal stress biomarkers to evaluate their application in assessing health risks for mothers and fetuses.

Material and Methods: This literature review examines clinical trials and observational studies from the late 20th and early 21st centuries. It focuses on laboratory techniques such as ELI-SA, HPLC, and radioimmunoassay used to measure stress markers in maternal serum, cord blood, amniotic fluid, and urine.

Results: Studies show that copeptin levels rise significantly during fetal hypoxia and IUGR, aiding ultrasonographic differentiation. Maternal cortisol levels correlate negatively with birth weight and increase the risk of infants being small for gestational age (SGA). ACTH and CRH serve as indicators of HPA axis maturity and predictors of preterm birth. Regarding non-hormonal markers, malondialdehyde and 8-isoprostane are sensitive indicators of oxidative stress linked to preeclampsia. Furthermore, elevated proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-alpha) are closely associated with intrauterine infections and the onset of preterm labor.

Conclusions: Perinatal stress biomarkers offer significant prognostic value for identifying risks of preterm labor and developmental pathologies. While cortisol currently has the greatest clinical utility, copeptin and malondialdehyde are noted for their stability and potential for routine screening. Further clinical trials are necessary to integrate these markers into standard obstetric care.

KEYWORDS

Perinatal Stress, Biomarkers, HPA Axis, Cortisol, Copeptin, Oxidative Stress, Preterm Labor

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1. Introduction

Ubiquitous stress affects many spheres of our lives. There are certain social groups whose exposure to chronic and/or severe stress can lead to much more serious complications than in the rest of the population. Pregnant women certainly constitute such a group. Pregnancy itself is a potent stressor that activates the neuroendocrine response of the future mother. Stress increases gradually during its course, reaching a climax during labor and the entire perinatal period. Natural, endogenous biomarkers secreted by the body in response to stress do not currently play a key role in gynecological diagnostics (Mulder et al., 2002).

The aim of this paper is to collect and analyze the latest scientific reports regarding perinatal stress biomarkers. Research teams worldwide are analyzing the properties and potential applications of these signaling molecules for the prospective assessment of health disorder risks in the mother and fetus resulting from stress exposure.

2. Hormonal markers of perinatal stress

2.1 Copeptin

Perinatal infections cause over one million neonatal deaths annually. Perinatal stress biomarkers are intended to potentially improve the effectiveness of early diagnosis of diseases threatening the child. Elevated copeptin concentrations in neonatal umbilical cord blood may be linked to various stressful situations, such as infections. Schlapbach et al. evaluated the impact of asphyxia on the levels of this biological marker. During labor, umbilical cord blood was routinely collected from the studied neonates into Ethylenediaminetetraacetic Acid (EDTA) tubes. Copeptin concentration was determined using an enzyme-linked immunosorbent assay—

sandwich Enzyme-Linked Immunosorbent Assay (ELISA). A statistically significant negative correlation was noted between the amount of copeptin in the neonate's serum and the pH of the umbilical cord blood ($r = -0.34$, $p < 0.0001$), which likely suggests that copeptin is secreted in increased quantities during fetal hypoxia. Schlapbach et al. demonstrated that copeptin may serve as an important perinatal stress marker in cases of conditions posing a real threat to the neonate's life, such as asphyxia or hypoxia (Schlapbach et al., 2011). Intrauterine growth restriction (IUGR) is a condition in which the fetus does not reach the appropriate birth weight. It should be differentiated from pathological entities such as SGA (small for gestational age) or reduced AC (abdominal circumference). IUGR occurs relatively rarely (1:10). The regulation of fetal growth is a complex process based on maternal-fetal-placental interactions. Prolonged stress causes persistent hyperglycemia, resulting from the action of cortisol, which inhibits glucose uptake by tissues. Fetal cells, deprived of their primary nutrient, divide more slowly, and weight gain is limited. In this way, intrauterine growth restriction may develop. Alizzi conducted a prospective clinical study aimed at verifying whether copeptin concentration measurements in the blood could distinguish IUGR from other pathologies with similar symptoms. Patients underwent medical diagnostics, including basic and Doppler ultrasonography (measurement of resistance and pulsatility indices in the umbilical artery). Based on the results, they were assigned to specific study groups. The control group consisted of mothers whose fetuses showed no pathology -appropriate for gestational age (AGA). Pregnant women whose children were diagnosed with SGA formed the first study group, while the remaining qualified women were placed in the second research group (children with IUGR). Venous blood was collected from the patients, and umbilical cord blood from the neonates. Serum copeptin concentration was examined using an enzyme immunoassay. According to the results, mean C-terminal pro-arginine vasopressin (CT-proAVP, copeptin) concentrations in both maternal serum and umbilical cord blood were significantly higher in study group II compared to study group I and the control. All obtained correlations were statistically significant ($p < 0.001$). Furthermore, the author observed a negative correlation between maternal blood copeptin levels and the previously mentioned Doppler ultrasound indices. The conclusions formulated by Alizzi suggest that copeptin is a very important diagnostic marker. Determining its serum concentration could become an auxiliary method for the ultrasonographic differentiation of intrauterine growth restriction in the developing fetus from similar disease entities (Alizzi & Bardan, 2018).

While the diagnostic value of copeptin in conditions like asphyxia and IUGR has been well established, its prognostic scope continues to expand. The latest scientific reports further highlight the clinical versatility of copeptin as a dynamic biomarker for various forms of perinatal stress and severe neonatal complications. Research by Wellmann et al. demonstrated that vaginal birth induces a profound secretion of copeptin compared to elective cesarean sections. This indicates that while arginine vasopressin (AVP) signals acute stress, copeptin effectively reflects cumulative stress events over a more extended perinatal period (Fill Malfertheiner et al., 2021). Furthermore, copeptin has proven valuable in assessing the severity of complications in premature infants. Flahault et al. revealed that elevated plasma copeptin in very preterm neonates strongly correlates with a more severe neonatal course—particularly the development of bronchopulmonary dysplasia—and is associated with long-term systemic consequences, such as smaller kidney volume in adulthood (Flahault et al., 2022). In the context of severe infections, recent meta-analyses emphasize that copeptin levels rise significantly during ischemic events and sepsis. According to Bhattarai et al., elevated copeptin serves as an excellent predictor of short-term mortality and a robust surrogate marker for overall disease severity in critically ill patients, including neonates with sepsis syndromes (Bhattarai et al., 2024).

2.2 Corticotropin-Releasing Hormone (CRH)

Despite numerous new achievements in medicine and technology over the past several decades, the percentage of children born preterm remains relatively high. This problem affects countries with high and low social development indices to a comparable degree. Preterm infants with low birth weight who survive the perinatal period are significantly more likely to suffer from respiratory diseases, experience cerebral palsy, or have difficulties with concentration and the learning process. Multicenter studies have confirmed that prenatal stress and anxiety can significantly shorten the duration of pregnancy (by an average of 1–3 weeks). Corticotropin-releasing hormone (CRH) secreted by the hypothalamus can affect the action of other hormones such as oxytocin or prostaglandins, which are primarily responsible for the contractility of uterine smooth muscles. Specific receptors for CRH are located on the surface of this organ's muscular layer, known as the myometrium. Their number increases in the perinatal period, sensitizing the uterine musculature to the action of CRH. The presence of CRH stimulates the release of prostaglandins from both the fetal membranes and the placenta, and potentiates the effect induced by oxytocin (Mancuso et al., 2004).

2.3 Adrenocorticotrophic Hormone (ACTH)

Authors rarely address adrenocorticotropin as a perinatal stress marker in their works. This stems from the fact that the most accurate and reliable results are obtained by collecting umbilical cord blood directly from the fetus using cordocentesis. This is an invasive method involving a puncture through the mother's abdominal walls under ultrasound guidance. This procedure is not performed routinely in every pregnant woman. Bagnoli et al. determined the effect of ACTH concentration on pregnancy duration and the impact of the delivery method on changes in this hormone's concentration. The study group included only children born via natural vaginal delivery (VD) or Cesarean section (CS). Immediately after birth, blood was collected from the umbilical vein. Serum was prepared, in which ACTH concentration was determined using an enhanced enzyme immunoassay utilizing chemiluminescence. Bagnoli et al. demonstrated a statistically significant positive correlation between ACTH concentration in umbilical cord blood serum and gestational age, both in the group of neonates born naturally ($p = 0.01$) and those born via Cesarean section ($p = 0.00001$). The HPA axis plays a key role in the body's response to stress. During the fetal period, the task of ACTH is to stimulate the adrenal cortex to properly shape internal regulatory mechanisms. Cortisol secreted by the adrenals is intended to adapt the neonate's body to stressful conditions. In preterm infants, the function of the HPA axis is not yet fully regulated (lower ACTH concentrations than in term infants), resulting in a diminished protective effect against stress. Measuring ACTH concentration in fetal serum obtained via cordocentesis could provide information on the degree of development of the regulatory HPA axis (Bagnoli et al., 2013). Economides et al. investigated the correlation between ACTH concentration in umbilical cord blood serum and the occurrence of SGA. Samples were obtained via cordocentesis, giving the researchers a real reflection of the hormone's concentration in the fetal body during pregnancy. Fetuses with an appropriate weight for gestational age (AGA) served as the control group, while fetuses diagnosed with SGA formed the study group. ACTH concentration was determined twice in both groups—at the beginning of the 18th and 36th weeks of pregnancy—using an enzyme immunoassay. The results obtained by Economides et al. allowed for two conclusions. Between the two measurement points, the mean ACTH concentration increased in both study groups. It was also observed that in fetuses with SGA, the ACTH level was significantly lower compared to the group without pathology. Thus, it can be assumed that measuring ACTH concentration via cordocentesis could be an alternative diagnostic method, alongside ultrasonography, to confirm the occurrence of fetal deviations from normal birth weight (Economides et al., 1988).

Maternal psychosocial stress significantly elevates ACTH levels, which subsequently signals the release of glucocorticoids and alters the intrauterine environment, potentially impacting fetal neurodevelopment and long-term biological programming (Fenster et al., 2020; Joseph & Whirledge, 2017). In acute clinical scenarios, such as fetal hypoxemia, ACTH concentrations rise markedly and correlate with markers of central nervous system cellular damage, establishing its validity as a strong indicator of compromised fetal oxygenation (Giussani, 2010). Furthermore, severe or prolonged stress can disrupt the HPA axis's negative feedback mechanisms, leading to massive ACTH elevations and compensatory adrenal hypertrophy (Cole et al., 1995).

2.4 Cortisol

In addition to the indirect influence of the external environment, various internal factors can exert unfavorable effects on the developing fetus. These include maternal comorbidities accompanying pregnancy (metabolic, cardiovascular, psychiatric). It is widely believed that low birth weight is the primary factor predisposing neonates to health complications during postnatal development. Numerous studies have been conducted to demonstrate the relationship between the mother's psychosocial state and the child's birth weight and the risk of SGA. High stress levels cause excessive stimulation of the HPA axis, leading to its dysregulation. This results in increased blood cortisol levels. Excessive amounts of this hormone inhibit fetal cell proliferation. Geertje Goedhart-de Wolf et al. evaluated the relationship between maternal cortisol concentration and infant birth weight in a large prospective cohort study. Cortisol concentration was determined in serum using a radioimmunoassay, while the psychological condition of the pregnant women was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D). Sociodemographic data were obtained from pregnancy surveys. Standardized mean cortisol concentration showed a negative correlation with neonatal birth weight ($r = -0.35$, $p < 0.001$). This was most evident in patients with the highest stress hormone concentrations. Higher cortisol levels were associated with an increased risk of SGA in the neonate (OR = 1.00, $p = 0.027$). Based on the statistical data, it was found that older women and those from higher social classes had significantly lower cortisol levels. Higher concentrations of this glucocorticoid were

observed in mothers whose children had low birth weight, were classified as SGA, or were female. In summary, measuring maternal serum cortisol could provide important information regarding the expected birth weight of the neonate (Goedhart et al., 2010).

Elevated maternal cortisol, particularly during early gestation, significantly alters fetal brain development—such as increasing amygdala volume—which predisposes offspring to emotional dysregulation and affective disorders (Buss et al., 2012). Beyond fetal impacts, exaggerated pre-pregnancy cortisol reactivity is a strong predictor of maternal postpartum depression (Beech et al., 2023).

2.5 Epinephrine and Norepinephrine

It has been proven that low birth weight or preterm birth can be prognostic factors for cardiovascular disease in adulthood. In young people who were preterm infants, anatomical and functional changes in blood vessel structure and elevated blood pressure are very frequently diagnosed. Maternal stress exposure may cause subsequent sympathomimetic system overactivity in the child. Johansson et al. decided to investigate catecholamine concentrations, heart rate (HR), and blood pressure (BP) in three groups of neonates: preterm (PT), term born with weight inappropriate for gestational age (SGA), and term born with appropriate birth weight (AGA). This was a cohort observational study where AGA children served as the control. Morning urine was collected from all neonates. Creatinine clearance was also examined to confirm the reliability of other results. Catecholamine concentrations were determined using high-performance liquid chromatography (HPLC). Resting HR and BP were measured in a supine position with the right arm flexed at the elbow, at heart level, using an automated oscillometric technique. The study authors showed that PT group children excreted larger amounts of both catecholamine metabolites in urine compared to the control group ($p = 0.02$ for epinephrine, $p = 0.11$ for norepinephrine). It was also observed that mean resting HR was higher in both the PT (76 bpm) and SGA (79 bpm) groups compared to the AGA group (70 bpm) ($p < 0.05$). Johansson et al. found significant positive correlations between HR and systolic BP ($r = 0.18$, $p = 0.065$), diastolic BP ($r = 0.24$, $p = 0.014$), urinary epinephrine metabolites ($r = 0.24$, $p = 0.04$), and urinary norepinephrine metabolites ($r = 0.27$, $p = 0.01$). Hypertension or coronary artery disease develops gradually throughout life. However, these disease entities will not affect everyone; their manifestation is influenced by both environmental and genetic factors. The ability to identify individuals with an increased risk of cardiovascular disease based on their birth weight or prematurity would offer these people a chance for effective primary prevention or timely pharmacotherapy (Johansson et al., 2007). In acute clinical scenarios, massive epinephrine elevations provide an objective measure of severe fetal compromise; for instance, median adrenaline levels can reach as high as 14,188 pg/ml in stillbirths, correlating directly with cellular damage markers such as S100beta (Giorgetti et al., 2024).

2.6 Progesterone

In scientific research to date, the potential utility of progesterone as a perinatal stress marker is rarely verified. Nevertheless, the results of a few studies confirm that it may have applications in gynecological diagnostics. Chiba et al. evaluated the correlation between serum progesterone concentration and the child's health status. Basic data on the pregnant women and the course of their pregnancies were collected. Serum was derived from umbilical cord blood collected at birth. Progesterone concentration was determined using an enzyme immunoassay (ELISA). The mean progesterone concentration in the group of neonates of non-smoking mothers was lower than in the group of neonates of smoking mothers ($p < 0.05$). In the group of neonates who achieved a maximum score (10 points) on the APGAR scale used to assessment performed by healthcare providers after birth to evaluate a newborn's physical condition (heart rate, respiration, muscle tone, reflexes, color of skin) at 1 minute, a significantly lower mean progesterone concentration was measured compared to the group of neonates who scored 8 points ($p < 0.017$, $r = -0.86$). Mean progesterone concentration also showed positive correlations with hemoglobin ($r = 0.49$) and insulin levels ($r = 0.45$). Fetuses exposed to stress secrete larger amounts of progesterone, likely linked to the body's defense against hypoxia (Chiba et al., 2010).

3. Non-hormonal markers of perinatal stress

3.1 Malondialdehyde

Even in a properly progressing pregnancy, excessive production of free radicals or impaired elimination from the body can occur. Such a state increases the risk of developing certain diseases. Based on several large clinical studies, it has been proven that oxidative stress is the main factor responsible for the development of pregnancy-induced hypertension. The pathomechanism of this phenomenon lies in the destructive influence of free radicals on the pregnant woman's vascular endothelium. This leads to an increase in peripheral resistance and elevated blood pressure (Krasomski et al., 2007).

It is suspected that lipid peroxidation of biological membranes, free radical formation, and disruption of antioxidant systems contribute to the development of preeclampsia, which is one of the leading causes of perinatal morbidity and mortality (AYDIN BERKTAŞ & TUTAR, 2022; Quilantán-Cabrera et al., 2026). Madazli et al. determined malondialdehyde concentrations in maternal serum and placental tissues of pregnant women with diagnosed preeclampsia using spectrophotometry. Normotensive patients served as the control group. Serum malondialdehyde levels in women with preeclampsia were statistically significantly higher ($p < 0.001$) than in women with normal blood pressure. An even greater difference in the amount of this oxidative stress biomarker was found in the placental tissues of patients with preeclampsia compared to normotensive pregnant women ($p < 0.001$). The results indicate a correlation between preeclampsia and the intensity of oxidative stress during pregnancy. Observations also suggest that malondialdehyde may be an effective measure of this process's intensification (Madazli et al., 2002).

3.2 Proinflammatory cytokines

In the last decade, many researchers have focused on determining the involvement of proinflammatory cytokines in the initiation of preterm labor (Raghupathy, 2008). Keelan et al. noted that proinflammatory cytokines secreted in response to intrauterine reproductive tract infection could influence the premature termination of pregnancy. This study evaluated cytokine concentrations in amniotic fluid. The results showed elevated concentrations of interleukins (1, 6, 8) and tumor necrosis factor alpha (TNF-alpha) in women who gave birth prematurely due to intrauterine infection (Keelan et al., 1999). Cervical secretions or fragments of amniotic or chorionic tissues can also serve as research material. Inglis et al. proved that elevated concentrations of gamma-interferon, TNF-alpha, and interleukins in the aforementioned biological material correlated with preterm delivery due to intrauterine infection (Inglis et al., 1994). Romero et al. suggested that the presence of pathogenic microorganisms causing infection forces the pregnant woman's body to produce cytokines, which through unspecified mechanisms initiate labor (Romero et al., 1998). In preterm births not complicated by reproductive tract infection, elevated concentrations of proinflammatory cytokines, especially interleukins (1, 6, 8), were also observable (Arntzen et al., 1998).

3.3 Isoprostanes

8-isoprostane is one of the best-studied representatives of the isoprostane group. Determining its plasma concentration allows for estimating the total endogenous pool of isoprostanes. Oxidative stress is an inherent element of every pregnancy. It has been found that oxidative stress intensification occurs in women whose pregnancies are complicated by other disease entities. Gubaljevic et al. decided to examine oxidative stress intensity in the first and second trimesters of pregnancy by measuring 8-isoprostane concentration and the resulting health consequences for the mother and child. A case-control study was conducted involving both pregnant and non-pregnant women. The study group was divided into two subgroups consisting of women in the first trimester and women in the second trimester. Healthy, fertile women served as the control group. 8-isoprostane concentration was determined in the urine using an immunological method. The mean concentration was significantly higher in pregnant women than in non-pregnant women. In both the first and second trimesters, this difference was statistically significant ($p < 0.0001$). It was also found that the increase in mean 8-isoprostane concentration between the first and second trimesters was statistically significant ($p < 0.005$). Gubaljevic et al. also observed that women with the highest individual 8-isoprostane levels often developed preeclampsia. Thus, it can be concluded that 8-isoprostane is a very sensitive marker of oxidative stress in pregnant women, and determining its concentration in urine provides the physician with more information about the current state of the patient and her child, potentially highlighting the risk of preeclampsia (Gradašević Gubaljević & Čaušević, 2013).

4. Conclusions

Among the biomarkers described in this work, cortisol appears to have the greatest clinical utility. It is the final compound in the regulatory pathway of the HPA axis, which is stimulated in response to a stressor. According to recent studies, its physiological action is primarily responsible for the body's adaptation to stressful conditions. A disadvantage of this biomarker is its secretion according to a circadian rhythm and the necessity of standardizing collected samples. The two most stable biological markers are copeptin and malondialdehyde. Copeptin is a promising biomarker that could provide valuable information to the obstetrician. Malondialdehyde shows high sensitivity to changes in oxidative stress intensity in the pregnant woman's body, suggesting it could be included in routine pregnancy screening. Isoprostanes exhibit similar sensitivity. Hypothalamic and pituitary hormones, CRH and ACTH, are characterized by a short biological half-life in the blood. However, CRH is recognized as one of the main prognostic factors for preterm birth, making its plasma concentration measurement of high diagnostic value. For ACTH, the most reliable results are obtained via cordocentesis. This is an invasive method that, if performed incorrectly, may pose a threat to the fetus. These facts mean that ACTH measurement is not considered a high-power diagnostic method. Determining catecholamine concentrations, according to the latest research, has high diagnostic potential in the prevention of future cardiovascular diseases. Their position should be consolidated by further clinical trials in this area. Proinflammatory cytokines are the least stable biomarkers. Despite this, their clinical utility in determining the mental state of the pregnant woman or the risk of preterm labor may be.

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