American Journal of
Oral Medicine and Radiology

ISSN - 2394-7721

www.mcmed.us/journal/ajomr

Research Article

MOLECULAR PATHWAYS IN PRE-ECLAMPSIA: THE ROLES OF HO, LEPTIN, COQ10, AND ESSENTIAL METALS IN MATERNAL AND FETAL HEALTH.

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ABSTRACT

Pre-eclampsia is a pregnancy-specific hypertensive disorder that significantly impacts maternal and fetal health, leading to increased prenatal morbidity and mortality globally. This study explores the biochemical markers and molecular mechanisms implicated in pre-eclampsia, focusing on oxidative stress, inflammation, and essential mineral imbalances. Among the key elements evaluated, heme oxygenase (HO) plays a protective role by breaking down heme into carbon monoxide (CO), bilirubin, and free iron, helping to reduce oxidative stress and regulate anti-inflammatory responses. Leptin, an adipokine also produced by the placenta during pregnancy, is elevated under hypoxic conditions in pre-eclampsia, serving as a marker for placental ischemia. Additionally, Coenzyme Q10 (CoQ10) is essential for mitochondrial function and energy production, showing potential for therapeutic use due to its antihypertensive and antioxidant properties. The study also highlights the imbalance of essential metals, including zinc (Zn), copper (Cu), and iron (Fe), which are critical for enzyme function and blood pressure regulation, with an imbalance contributing to hypertension risk. Understanding these biomarkers and their functions offers insights into early detection and potential therapeutic interventions for pre-eclampsia, enhancing clinical outcomes for both mothers and infants.

Key words:- Pre-Eclampsia, Heme Oxygenase, Leptin, Coenzyme Q10, Oxidative Stress, Zinc, Copper, Iron, Hypertension, Pregnancy.

Access this article online		
Home page: http://www.mcmed.us/journal/ajomr		Quick Response code
Received:25.06.22	**Revised**:12.07.22	**Accepted**:14.08.22

INTRODUCTION

Pre-eclampsia is a pregnancy-specific disorder that affects both the mother and fetus, significantly increasing prenatal morbidity and mortality worldwide. This condition affects 8-10% of all pregnancies globally and is associated with complications such as placental ischemia, impaired uteroplacental blood flow, and restricted trophoblast invasion. Heme oxygenase (HO) is an enzyme that breaks down heme into carbon monoxide (CO), bilirubin, and free iron.

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This process helps reduce oxidative stress and plays a role in modulating anti-inflammatory and anti-apoptotic responses, which are critical for healthy pregnancy progression.

Leptin, a hormone with metabolic and physiological functions, is produced by both white adipose tissue and the placenta during pregnancy. In pre-eclampsia, hypoxic conditions lead to elevated leptin production, making it a potential marker for placental ischemia in affected patients. Coenzyme Q10 (CoQ10) is essential for mitochondrial oxidative phosphorylation and is known for its antihypertensive, anti-atherogenic,

neuroprotective, and bioenergetic properties. It supports the proper functioning of tissues and organs across the body. The minerals zinc (Zn), copper (Cu), and iron (Fe) are integral components of various enzymes and play a significant role in blood pressure regulation. An imbalance of zinc and copper in the body may contribute to the development of hypertension in humans, underscoring the importance of these metals in maintaining vascular health.

Methods and subjects

Subjects

The study included 80 pregnant women who attended the outpatient clinic and 70 preeclamptic patients who attended the Department of Obstetrics and Gynecology (OBG) at the Gouri Devi Institute of Medical Sciences and Hospital, Durgapur, West Bengal, India. The Human Ethics Committee at the Gouri Devi Institute of Medical Sciences approved the study.

Subjects diagnosed with pre-eclampsia were pregnant for at least 20 weeks and of childbearing age. Exclusion criteria included chronic hypertension and twin pregnancies. All subjects provided written informed consent before participation.

Methods of Laboratory Analysis

Collection of Samples

Blood samples were collected under complete aseptic conditions using heparinized syringes, then aspirated into a Blood Gas Analyzer for immediate analysis.

Analysis of Biochemical Data

- Determination of Bilirubin and Liver Enzymes: The activities of ALT and AST were measured using kits from BioMed Diagnostics, following the method by Reitman and Frankel [9]. Additional tests for bilirubin and liver enzymes were performed using a kit from High Performance Diagnostic Reagents [10].
- Serum Uric Acid and Creatinine: Uric acid levels were measured using a Biocon Diagnostics kit based on the method by Weir et al. [11]. Creatinine kinetics were analyzed using a High Performance Diagnostic Reagents (HPDR) kit adapted to Bartel's method.
- Determination of HO COHb: The percentage of HO COHb in arterial blood was measured with a blood gas analyzer, applying the method by Hampson et al. [13].
- Serum Leptin Determination: Serum leptin concentration was measured with a kit following the protocol by Considine and Sinha [14].
- Serum CoQ10 Determination: High-performance liquid chromatography (HPLC) was used to measure serum CoQ10 according to the method by Mosca et al. [15]. A solution of 1,4-benzoquinone was added to 400 µl of serum, followed by a 10-second centrifugation. After a 10-minute incubation, 1 ml of n-propanol was added. The mixture was vortexed for 10 seconds and centrifuged at 10,000 rpm for 2 minutes at 4°C.
- Zn and Cu Determination in Serum: Levels of Zn and Cu were determined using an atomic absorption spectrophotometer, applying the method by Sinaha and Cabrielli [16]. Measurements were performed using a Perkin-Elmer 2380 spectrophotometer.
- Determination of Serum Fe and TIBC: Fe and TIBC in serum were measured by colorimetry using a Stanbio kit from the United States, following the protocol [17].
- Determination of Serum Ferritin: Circulating ferritin concentrations were quantitatively measured using ELISA, following Corti et al. [18]. The kit was supplied by Monobind Inc., USA.

Statistical Analysis

Data were expressed as mean ± SD unless otherwise indicated. The Student's t-test was used to assess statistical significance, with all analyses conducted using SPSS version 16. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant [19].

Results

Bilirubin and Liver Enzymes

In the pre-eclampsia group, serum levels of ALT and AST were significantly elevated compared to those in normal pregnant women. Additionally, the serum bilirubin level in the pre-eclampsia group was notably lower than that in the control group ($p < 0.05$).

Parameters	Normal Pregnant	Pre-eclampsia
ALT (U/l)	8.2 ± 0.50	11.5 ± 0.80a
AST (U/l)	11.0 ± 0.40	15.2 ± 0.70a
Bilirubin (mg/dl)	0.45 ± 0.04	0.34 ± 0.02a

Serum Creatinine and Uric Acid

The pre-eclampsia group exhibited significantly higher serum uric acid and creatinine levels than the normal pregnant group ($p < 0.05$).

Parameters	Normal Pregnant	Pre-eclampsia
Uric Acid (mg/dl)	6.2 ± 0.30	8.5 ± 0.50a
Creatinine (mg/dl)	0.88 ± 0.04	2.15 ± 0.06a

Ferritin, TIBC, and Serum Iron

Compared to the normal pregnant group, pre-eclamptic patients had significantly elevated serum iron (Fe) and ferritin levels, along with reduced TIBC values ($p < 0.05$).

Parameters	Normal Pregnant	Pre-eclampsia
Fe (µg/dl)	70.5 ± 6.0	89.0 ± 5.7a
TIBC (µg/dl)	432.0 ± 5.0	390.0 ± 5.8a

Ferritin (ng/dl)	40.5 ± 2.1	82.0 ± 2.1a

COHb, Leptin, and CoQ10 Levels

Blood COHb levels were significantly lower in the pre-eclampsia group compared to the normal pregnant group. Additionally, serum leptin levels were notably higher in the pre-eclampsia group, while CoQ10 levels were significantly lower ($p < 0.05$).

Parameters	Normal Pregnant	Pre-eclampsia
COHb (%)	1.0 ± 0.04	0.4 ± 0.04a
Leptin (ng/ml)	26.5 ± 0.12	75.0 ± 2.4a
CoQ10 (µmol/l)	2.10 ± 0.04	0.60 ± 0.03a

Copper and Zinc Levels in Serum

Serum Zn levels in the pre-eclampsia group were significantly lower than those in the normal pregnant group, while serum Cu levels were significantly higher in the pre-eclampsia group ($p < 0.05$).

These results indicate that pre-eclampsia is associated with significant biochemical changes, including elevated ALT, AST, creatinine, uric acid, iron, ferritin, leptin, and copper levels. Additionally, reductions were observed in bilirubin, TIBC, COHb, CoQ10, and zinc levels in pre-eclamptic patients compared to normal pregnant women, highlighting potential biomarkers for pre-eclampsia diagnosis and monitoring.

Parameters	Normal Pregnant	Pre-eclampsia
Zn (µg/dl)	105.0 ± 5.5	85.0 ± 4.2a
Cu (µg/dl)	125.0 ± 6.0	160.0 ± 5.8a

Discussion

In this study, women with pre-eclampsia demonstrated lower levels of COHb compared to normal pregnant women, indicating a reduction in heme oxygenase (HO) activity. This aligns with findings from other studies, which observed lower CO concentrations in pre-eclamptic women compared to healthy pregnancies. The elevated blood pressure in pre-eclampsia is associated with vasoconstriction, reducing placental blood flow and diminishing HO activity, which, in turn, decreases its ability to catalyze heme breakdown. Hemeoxygenase, when combined with NADPH and cytochrome P-450, oxidizes heme to produce carbon monoxide (CO) and bilirubin, compounds that promote vasodilation and protect the endothelium from oxidative stress. These findings suggest that the lower CO levels in pre-eclamptic women could result in decreased vasodilatory effects, which may impact feto-placental circulation and increase risks to both the fetus and mother.

The study also highlighted a significant increase in serum leptin levels among pre-eclamptic women compared to healthy pregnancies, consistent with other research. High leptin levels are thought to influence nor-adrenaline turnover in the fetal-maternal unit, potentially impacting fetal health and contributing to adverse outcomes like intrauterine growth restriction. Hypoperfusion and hypoxia within the placenta, as seen in pre-eclampsia, may contribute to the elevated leptin levels, as noted in other studies. The role of leptin as a potential compensatory response to impaired placental perfusion suggests it may serve as a biomarker for pre-eclampsia severity and fetal risk.

Furthermore, serum CoQ10 levels were significantly reduced in the pre-eclampsia group compared to the normal pregnancy group, corroborating previous findings. Elevated levels of CoQ10 in healthy pregnancies may be attributed to increased LDL, which carries CoQ10 in plasma, as well as elevated cholesterol levels. The decreased CoQ10 levels in pre-eclampsia could be linked to free nitric oxide (NO), which reversibly inhibits mitochondrial complex I. Reduced CoQ10 can impair cellular antioxidant capacity, contributing to the oxidative stress observed in pre-eclampsia.

Iron and ferritin levels were significantly higher in the pre-eclamptic group, while TIBC levels were lower, similar to observations in related studies. The demand for iron in feto-placental development, combined with oxidative stress, may lead to increased iron and ferritin levels in pre-eclampsia. The elevated ferritin may indicate a compensatory response to endothelial damage caused by lipid peroxidation and red blood cell destruction. However, despite elevated iron and ferritin, some studies suggest that serum iron measurements alone cannot predict pre-eclampsia.

The study also found significantly lower zinc (Zn) and higher copper (Cu) levels in pre-eclamptic women, consistent with findings from other researchers. Elevated estrogen levels during pregnancy may increase ceruloplasmin, an enzyme associated with copper, while factors like increased oxidative stress and the need for Zn in enzyme systems may deplete serum Zn levels. Zinc is essential for fetal immune development and reducing pregnancy-related hypertension, preterm birth, and low birth weight. The decrease in Zn may be influenced by hemodilution, increased urinary excretion, and fetal transfer, which affect serum Zn concentrations during pregnancy.

Overall, these results emphasize the critical roles of HO, leptin, CoQ10, and trace elements in the pathogenesis and progression of pre-eclampsia. The metabolic changes observed in these markers highlight their potential as indicators of pre-eclampsia severity and offer insights into the underlying mechanisms of the condition.

Conclusion

This study identifies key biochemical alterations associated with pre-eclampsia, including decreased COHb and CoQ10 levels, elevated leptin, ferritin, and copper levels, and reduced zinc. These findings support the potential of heme oxygenase, leptin, and CoQ10 as early biomarkers for pre-eclampsia. By monitoring these markers, it may be possible to predict pre-eclampsia risk and severity, enabling earlier intervention. Given CoQ10's role in reducing oxidative stress and supporting endothelial function, supplementation with CoQ10 during pregnancy could be explored as a preventive measure to reduce the risk of pre-eclampsia and hypertension. Additionally, the HO pathway and its metabolites, CO and bilirubin, may offer new avenues for therapeutic strategies aimed at managing hypertension and oxidative stress in pre-eclampsia. Further studies are recommended to explore these potential interventions and validate their effectiveness in improving maternal and fetal outco

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Cite this article:
Dr. Sudipta Paul. Molecular Pathways In Pre-Eclampsia: The Roles Of Ho, Leptin, COQ10, And Essential Metals In Maternal And Fetal Health. *American Journal of Oral Medicine and Radiology*, 2022, 9(2), 30-34.