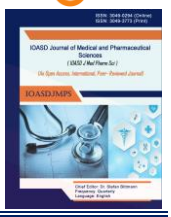
OPEN ACCESS

IOASD Journal of Medical and Pharmaceutical Sciences

IOASD J Med Pharm Sci, Vol-3, Iss-3, Jul-Sept., 2026
Frequency: Quarterly
ISSN: 3049-0294 (Online)
ISSN: 3049-3773 (Print)
Homepage: https://ioasdpublisher.com/ioasdjmps



Clinical Significance of Lipoprotein and Ceruloplasmin Variation in Preeclampsia

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DOI: 10.67224/ioasdjmps.2026.v03i03.018

ABSTRACT

Preeclampsia is a multisystem illness of pregnancy characterised by new-onset hypertension after 20 weeks of gestation and end-organ failure of varied severity. Placental dysfunction, maternal endothelial injury, inflammation, oxidative stress, and aberrant lipid metabolism are identified as significant features of the disease process, however the detailed pathophysiology is still not fully understood. Preeclamptic women have shown changes in circulating lipoproteins, including an increase in triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C). Ceruloplasmin is a copper-containing acute phase protein with key antioxidant and ferroxidase properties, which has also been shown to be increased in preeclamptic pregnancy. Meta-analysis of 15 trials and 1,927 women showed that serum ceruloplasmin concentrations were considerably higher in women with preeclampsia than in healthy pregnant controls. These biochemical abnormalities may reflect interplay between the dyslipidaemia, oxidative stress and endothelial dysfunction characteristic of preeclampsia. Thus, lipoprotein and ceruloplasmin assays may be beneficial to give us information on the metabolic and oxidative milieu accompanying the disease. But the evidence to date does not support their usage as a stand-alone diagnostic tool. Their greatest clinical utility may be in combination with established clinical indicators and other biochemical or placental biomarkers for risk stratification, illness monitoring and knowledge of pathogenesis.

Keywords: Preeclampsia; lipoproteins; triglycerides; HDL-C; LDL-C; ceruloplasmin; oxidative stress; endothelial dysfunction; biomarkers.

Review Article

Article History
Received: 07-07-2026
Accepted: 27-08-2026
Published: 01-09-2026

INTRODUCTION

Preeclampsia is one of the most important hypertension disorders of pregnancy and continues to be a significant cause of maternal and neonatal morbidity and mortality. The condition is characterised by aberrant placentation, poor remodelling of the maternal spiral arteries, placental ischaemia and subsequent release of substances promoting systemic maternal endothelial dysfunction. The clinical signs include hypertension, proteinuria, renal failure, hepatic involvement, neurological problems, haematological disorders and foetal development limitation [1].

The pathophysiology of preeclampsia is complicated and involves the interplay of placental anomalies, oxidative stress, inflammation, angiogenic imbalance, immunological dysfunction, metabolic changes and vascular endothelial damage. There is increasing evidence that aberrant lipid metabolism is not just a consequence of preeclampsia, but may play a role in the pathogenesis and progression of the condition. Dyslipidaemia may induce lipid peroxidation, inflammation and vascular damage and hence contribute to the endothelial dysfunction characterising preeclampsia [2].

Pregnancy itself causes physiologic changes in lipid metabolism. Maternal triglycerides, cholesterol and lipoproteins tend to increase as pregnancy advances to meet the energy and developmental needs of the foetus. However, women who develop preeclampsia may have an excessive or abnormal change in this lipid response. Preeclampsia was associated with increased total cholesterol, triglycerides and non-HDL cholesterol, and

reduced HDL-C, especially in the third trimester, according to a major meta-analysis [3].

More recent data continue to indicate a link between dyslipidaemia and preeclampsia. A comprehensive review and meta-analysis in 2025 revealed significantly reduced HDL and higher values of LDL, total cholesterol and triglycerides in women with preeclampsia compared with controls. In a major systematic analysis published in 2025, it was revealed that increases in LDL and HDL were not consistently observed throughout pregnancy until clinical diagnosis, although very-low-density lipoprotein (VLDL) was enhanced in studies addressing late pregnancy. In most research, after diagnosis in the third trimester, VLDL was increased while HDL decreased in many trials [4].

Another proposed molecular relationship between inflammation, copper metabolism and oxidative stress is ceruloplasmin. It is an acute phase protein produced mostly by the liver and responsible for the transfer of most circulating copper. It has ferroxidase activity that catalyses the conversion of ferrous to ferric iron, therefore minimising iron-mediated oxidative damage. As ceruloplasmin concentrations rise in inflammatory and oxidative states, changes in ceruloplasmin concentrations may be indicative of the physiologic milieu that accompanies preeclampsia.

A meta-analysis of 15 trials with 1927 women indicated that maternal serum ceruloplasmin levels were considerably higher in women with preeclampsia than in healthy pregnant women. The association of modified lipoprotein metabolism with elevated ceruloplasmin so suggests that these measures may reflect interrelated metabolic, inflammatory and oxidative mechanisms in preeclampsia [5].

Changes in Lipoproteins in Pre-Eclampsia

Cholesterol and triglycerides are transported around the circulation in lipoproteins. Major clinically relevant fractions are HDL, LDL, VLDL and intermediate density lipoprotein. Non-HDL cholesterol is the cholesterol in all potentially atherogenic particles. In uncomplicated pregnancy, lipid concentrations slowly increase. This physiological hyperlipidaemia is required for steroid hormone synthesis, placental function and foetal growth. In preeclampsia, however, lipid metabolism may be disrupted in a disproportionate manner. The most common pattern that has been documented is: high triglyceride levels; raise overall cholesterol; elevated LDL-C increased VLDL, higher non-HDL cholesterol; and low HDL-C, particularly in established or late-onset illness [6].

A recent meta-analysis found significant rise in triglycerides, LDL and total cholesterol and decrease in HDL among women with preeclampsia. A previous meta-analysis of 74 papers similarly indicated increased total cholesterol, non-HDL cholesterol and triglycerides with reduced HDL-C especially in the third trimester among women who had preeclampsia. The size and timing of these alterations are therapeutically relevant. Gestational age, body mass index, nutrition, insulin sensitivity and other metabolic variables have a considerable effect on lipid concentrations. Therefore, an abnormal lipid measurement cannot be automatically regarded as indication of preeclampsia [7].

Mechanisms Connecting Lipoproteins to Preeclampsia

There are numerous processes that can be considered to explain the association between dyslipidaemia and preeclampsia. Firstly, increased amounts of circulating lipids, particularly triglyceride-rich lipoproteins and LDL, can increase substrate availability for lipid peroxidation. Oxidised lipids can activate inflammatory processes and harm endothelial cells. It is thought that oxidative stress plays a crucial role in preeclampsia because the interplay between oxidation-prone lipids and placental or inflammatory factors may produce a cycle of oxidative injury and endothelial dysfunction. LDL, too, is highly vulnerable to oxidative alteration. Oxidised LDL can induce endothelial activation, inflammatory cell recruitment and vascular damage. Recent data has also implicated oxidised LDL receptor pathways and inflammatory signalling in pregnancy-associated endothelial dysfunction.

High triglycerides and VLDL may also lead to endothelial dysfunction and placental vascular anomalies. VLDL is particularly important as a recent systematic review showed evidence that it may be increased before clinical diagnosis of pre-eclampsia in late pregnancy. Besides HDL contains some vascular protective properties, like cholesterol efflux, antioxidant actions and control of inflammation. A decrease in HDL may thus result in less protection against oxidative and inflammatory vascular damage. The higher levels of atherogenic lipoproteins and the lower levels of the beneficial HDL produce a milieu that may promote endothelial dysfunction [8].

Preeclampsia and ceruloplasmin

Ceruloplasmin is a plasma glycoprotein containing copper with transport and enzymatic activities. Circulating copper is mostly related with ceruloplasmin, which is a crucial component of systemic copper homeostasis. Importantly, ceruloplasmin is also an acute phase reactant. It can be increased in response to inflammatory stimulation. Its ferroxidase activity promotes the oxidation of Fe^{2+} to Fe^{3+}, which favours iron binding to transferrin and could restrict the production of highly reactive oxygen species through iron-catalyzed processes. Thus, elevated ceruloplasmin in preeclampsia may be a consequence of inflammation and oxidative stress, not a major cause of illness. This connection is well supported by a meta-analysis. In 15 investigations including 1927 pregnant women, preeclampsia was associated with significantly increased

serum ceruloplasmin levels compared with healthy pregnant controls. The mean difference recorded was of about 12.57 mg/dL and was larger in both moderate and severe preeclampsia. Interestingly, the same meta-analysis did not find a statistically significant difference between mild and severe preeclampsia in ceruloplasmin. This is crucial because it indicates that while ceruloplasmin may distinguish preeclamptic from healthy pregnancy, it is not certain that it reflects illness severity accurately [10].

Ceruloplasmin, lipoproteins and oxidative stress: relationship

Lipoprotein abnormalities and elevated ceruloplasmin may not be independent results. Both may represent the underlying oxidative and inflammatory milieu of preeclampsia. Dyslipidaemia increases the availability of oxidation sensitive lipids while placental malfunction and systemic inflammation increase oxidative stress. Acute-phase proteins such as ceruloplasmin may rise in response to this environment. Ceruloplasmin may rise as part of the maternal acute-phase response and antioxidant defence system. The simultaneous determination of lipoproteins and ceruloplasmin may therefore provide more biological information than the determination of either parameter alone. Increased triglyceride/LDL profile with increased ceruloplasmin may indicate co-existence of metabolic disruption and systemic inflammatory/oxidative activation. But this view is not diagnostic, it becomes mechanistic. Prospective studies are needed to assess whether combined lipoprotein–ceruloplasmin profiles improve prediction beyond recognised clinical and biochemical markers [11].

Clinical Relevance

Lipid measurements are affordable, readily available and commonly conducted in clinical labs. They are interesting candidates for inclusion in risk-assessment procedures, because they are easily available. There is evidence that women who develop preeclampsia may have higher levels of triglycerides, total cholesterol and non-HDL cholesterol. However, lipid levels should be evaluated according to gestational age and maternal metabolic profile.

Second, serial measurements may provide information on changes in the maternal metabolic condition during pregnancy. Increasing triglycerides or worsening HDL/atherogenic lipid profiles may identify women requiring closer clinical evaluation. However, lipid testing should be used as an adjunct and not in substitution of blood pressure monitoring, urine protein assessment, assessment of maternal organ function and foetal surveillance [12].

Indeed, the constant finding of elevated ceruloplasmin in preeclampsia implies that it may be useful as an additional biomarker. The meta-analysis found that serum ceruloplasmin may be beneficial as a screening and follow up measure, but further study is needed to determine clinically relevant cut-off values, sensitivity and specificity. In fact, the greatest potential therapeutic relevance may lie in combining lipoproteins and ceruloplasmin with other biomarkers, rather than relying on an isolated laboratory assay. Preeclampsia is physiologically heterogeneous and no single biomarker accurately reflects its complicated pathophysiolog. A future prediction panel could potentially include: triglyceride; HDL-C; LDL-C; non-HDL-C or VLDL; ceruloplasmin: C reactive protein; uric acid; angiogenic biomarkers (e.g. sFlt-1 and PlGF); blood pressure readings; and maternal obstetric and demographic risk factors Also, biomarkers of oxidative stress are being studied as possible supplementary markers; data from systematic reviews suggests that markers such as malondialdehyde, uric acid and ischemia-modified albumin may be of diagnostic use but need further validation [13].

Limitations of the Current Evidence

There is compelling evidence that dyslipidaemia and ceruloplasmin are associated with preeclampsia, however various limitations need to be noted. Lipid levels are known to vary naturally during pregnancy. Gestational age at blood collection is therefore an important factor. A thorough analysis in 2025 showed several research did not effectively control for gestational age, restricting direct comparisons between studies [14]. Second, maternal BMI, obesity, insulin resistance, nutrition, diabetes and other metabolic disorders may alter lipid concentrations independent of preeclampsia. Third, the link of lipid abnormalities to preeclampsia may be bi-directional. Dyslipidaemia may contribute to illness development, but conversely, systemic inflammation and placental dysfunction associated with preeclampsia may also influence lipid metabolism. Fourth, the elevated ceruloplasmin is not specific for preeclampsia. As an acute phase protein, inflammatory circumstances may potentially raise its levels. Finally, connections are high, but neither standard lipid measures nor ceruloplasmin are now supported by adequate data to be a stand-alone diagnostic test for preeclampsia [15].

CONCLUSION

Changes in lipoproteins and ceruloplasmin are key biochemical characteristics of preeclampsia and might reflect interrelated abnormalities in lipid metabolism, inflammation, oxidative stress and endothelial function. Increasingly there is recognition that preeclamptic pregnancy is associated with an atherogenic metabolic profile characterised by increased triglycerides, total cholesterol, LDL-C and VLDL, with decreased HDL-C. Conversely, elevated blood ceruloplasmin may indicate the inflammatory and oxidative milieu associated with the disease, and meta-analytic research has demonstrated significantly greater quantities in women with pre-eclampsia.

Clinically, these characteristics are promise as supplementary biomarkers, not as standalone diagnostic tests. Integration with maternal clinical features, blood pressure readings, angiogenic markers and other biochemical indications could achieve full potential. Further prospective research should define reference values for each trimester, prediction cut-offs and combined biomarker algorithms. Such techniques may improve early risk categorisation and provide greater insight into the metabolic and oxidative pathways of preeclampsia.

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