Review Article

NEUTROPHIL - LYMPHOCYTE RATIO AS A BIO- INFLAMMATORY PROGNOSTIC MARKER OF FETOMATERNAL OUTCOMES OF PRE-ECLAMPSIA: a narrative review

ABSTRACT:

BACKGROUND: Pre eclampsia and its related complications are potent contributors to maternal mortality and morbidty. Early diagnosis and appropriate management of pre eclmapsia can prevent antenatal , intranatal and post natal complications associated with pre eclampsia. Neutrophil to lymphocyte ratio (NLR), which is calculated from complete blood count and dedifferentiation, is a simple and easily obtainable inflammatory index. (1) Accumulated studies have shown that NLR is indicator of Pre- eclampsia.

Objective of this nr In this we summarized the evidence regarding the clinical utility of NLR in pre eclampsia and its related complications.

METHODS: A comprehensive systematic search from PubMed, Embase, Cochrane Library, VIP database for relevant literature.

Sensitivity, specificity and other measures of accuracy of NLR for the diagnosis of PE were pooled.

Keywords: NLR, preeclampsia, fetomaternal outcomes, biomarker

INTRODUCTION: Why there is need to predict fetomaternal outcome ?

Preeclampsia occurs in 2–5% of pregnancies in the Occident, but it complicates up to 10% of pregnancies in the developing countries, where emergency care is often inadequate or lacking. Therefore we are in need of a widely applicable and affordable test that could permit presymptomatic diagnosis in order to identify and monitor the patients at risk and thus provide the best prenatal care for these women and their child. Such a test would also be of benefit to confirm a confounding clinical diagnosis and for future studies investigating prophylactic treatments or temporizing therapies.

To be effective a screening test need to be sufficiently sensitive and specific and must provide an adequate positive predictive value. Today, several promising markers have been described, alone or in combination, that might fulfill these criteria. However, these data came often from small case studies with selected populations.

Therefore, there is a need for worldwide large scale prospective studies to confirm the sensitivity and specificity of these promising markers and assess their utility in different subtypes of preeclampsia before they could serve in clinically useful screening tests.

What is "PRE-ECLAMPSIA"?

Preeclampsia is a multi-system disorder of pregnancy, which is characterized by new onset hypertension (systolic and diastolic blood pressure of ≥ 140 and 90 mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of ≥ 300 mg in a 24 h urine collection, or a dipstick of ≥ 2+), that develop after 20 weeks of gestation in previously normotensive women

Dependent on the systemic involvement, several other symptoms, such as edema, disturbance of haemostasis, renal or liver failure, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) also complicate the clinical picture. Preeclampsia can have an early onset (preeclampsia starting before 34 weeks of gestation) or late onset (preeclampsia starting after 34 weeks of gestation), can show mild or severe symptoms (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg, proteinuria >5 g/24 hours, oliguria, neurological symptoms, other clinical symptoms such as deranged liver function, thrombocytopenia < 100 000 mm3, HELLP syndrome), and can evolve in eclampsia in the most severe cases. In addition, it can manifest as a maternal disorder only, with an appropriate fetal growing, or it can present itself with a growth restricted fetus (intrauterine growth restriction (IUGR)) or sudden fetal distress.

Pathophysiology:

The precise origin of preeclampsia remains elusive, but it is believed to be likely multifactorial. A certainty is the central role played by the placenta in its pathology

A long standing hypothesis has been that preeclampsia develops as a consequence of some kind of immune maladaptation between the mother and the fetus during

the very first weeks of pregnancy, leading to a 2-step disorder progression (Figure 1.) that can be summarized as following: in a first – asymptomatic – step, local aberrant fetomaternal immune interactions within the uterine wall lead to impaired tissue and arterial invasion by trophoblast cells. This results in failed transformation of the uterine spiral arteries and subsequently worsened placental perfusion. Chronic hypoxia or alternate periods of hypoxia/re-oxygenation within the intervillous space is expected to trigger tissue oxidative stress and increase placental apoptosis and necrosis.

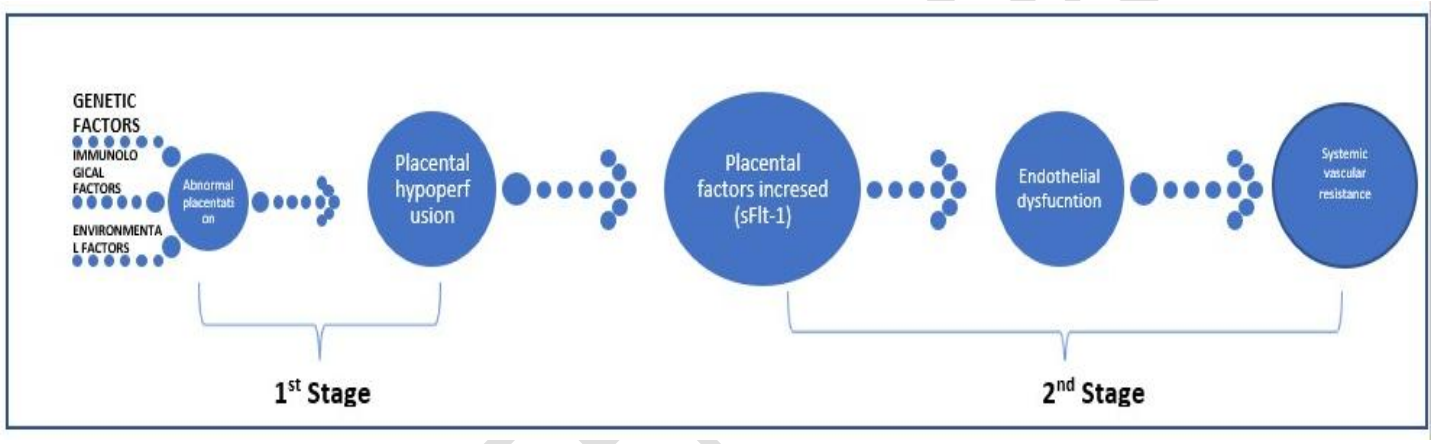

Figure 1.

Two-Stage Theory of Pre-eclampsia

The clinical disorder arises, in a second step, when the maternal vascular and immune systems cannot handle any longer the increased shedding of placental-produced debris and the aberrant expression of pro-inflammatory, anti-angiogenic and angiogenic factors and the activation of monocytes and neutrophils, leading to a systemic endothelial cell dysfunction and an exaggerated inflammatory response (1, 9, 10). The neutrophil plays an important role in the pathogenesis of PE. Activation of neutrophils occurs by exposure to oxidized lipids secreted by the placenta, when they pass the intervillous space. (2–4)

This leads to thrombocyte activation, vasoconstriction, hypertension, endothelial dysfunction, and end-organ ischemia. For this reason, the clinical stadium of PE is characterized by hypertension, proteinuria, edema, headache, scotoma, coagulopathy, and renal and hepatic dysfunction. Systemic inflammation occurs in normal pregnancies. There is a shift towards Th2 (suppressor T-helper) lymphocytes in normal pregnancies, which leads to suppression of Th1 cytokines,

which in turn enables maternal immune tolerance to the fetus, whereas in PE there is a shift towards the Th1 response, an immune maladaptation, and a hyper-inflammatory state.

It was proposed instead that intrinsic failure in trophoblast differentiation (Figure 2.) at different time points of ontogeny may lead to either a mild disorder with late-onset appearance, or IUGR complicated or not with the maternal symptoms.

However, the origin of preeclampsia might not be restricted to an alteration of trophoblast differentiation, but may also in some cases depend on an underlying maternal constitutional factors such as genetic, obesity, dysfunctional maternal clearance or inflammatory systems (12).

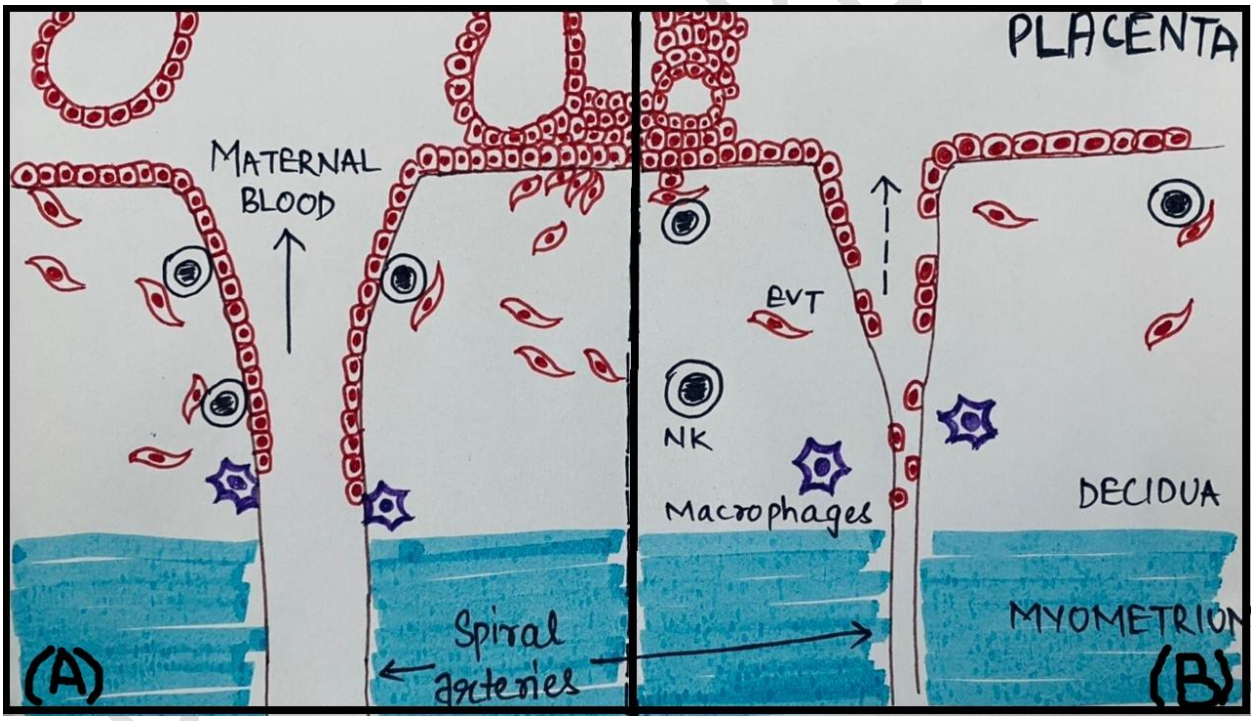

Figure 2.: Spiral arteries and trophoblast invasion in ***healthy*** (A) and ***preeclamptic*** (B) pregnancy.

Preeclampsia is characterized by shallow trophoblast invasion and defective vascular remodeling leading to reduced maternal blood flow, which in turn may compromise fetal growth. Failure of decidual natural killer (NK) cells and

macrophages (MΦ) to recruit trophoblast cells and support angiogenesis may contribute to the development of the disease. EVT: extravillous trophoblast

MATERIALS AND METHODS:

Using a series of keywords, we reviewed electronic databases (Medline, Elsevir) reporting the performance of biological markers to predict preeclampsia, both single markers and combinations of markers.

NEUTROPHIL-LYMPHOCYTE RATIO AS A BIOMARKER OF PRE-ECLAMPSIA:

1. Neutrophil-Lymphocyte Ratio as a Predictive Biomarker of Pre-eclampsia:

In the recent years, the neutrophil-to-lymphocyte ratio (NLR) has been used as systemic inflammatory response (SIR) markers. NLR has received much attention in the predictive value of several different diseases, such as cancer and heart disease. Leukocytes are increased in PE more as compared to normal pregnancy. There is a decrease in Lymphocytes and increase in Neutrophils which results in increased NLR in PE. In women with PE, it is likely that neutrophils are activated as they circulate through intervillous space and are exposed to oxidized lipids secreted by the placenta (5,6). Oxidized lipids are potent activators of neutrophils, leading to expression of COX-2 which regulates the release of thromboxane, TNF and superoxide (Vaughan et al., 2006; Vaughan and Walsh, 2005). Neutrophils obtained from preeclamptic females express significantly more COX-2 than neutrophils obtained from healthy pregnant females or healthy non-pregnant females (7).

In many studies, macrophages in atherosclerotic plaque are considered to have a role as foam cells. Lymphocytes are a part of the adaptive immune system with the production of antibodies to overcome diseases. Neutrophils are usually thought to be the first line of defence against infection at the site of a wound, but as has been reported in recent studies, neutrophils infiltrate systemic vascular tissue in women with pre-eclampsia, thus causing vascular inflammation (8,9). Other leukocyte types might also infilltrate the maternal vascular system in pre-eclamptic patients and may be responsible for vascular dysfunction

NLR is a simple and inexpensive inflammatory indicator, accumulated studies have investigated the clinical utility of NLR during pregnancy.

Two cross-sectional studies published in 2014 (10,11) investigated the relationship between NLR and PE, but the results are inconsistent. One study found that NLR in PE patients was higher than that in normal pregnant woman, and increased NLR was independently associated with PE after adjusting for cofounding factors (10). The other study determined the NLR level before the caesarean delivery but failed to find the increased NLR in PE (11). Subsequently, several cross-sectional studies have investigated the relationship between PE and NLR, and the results varied (4,12–17). Some studies found that NLR was higher in PE than in normal pregnant women (4,12,14–18), while one study failed to demonstrate a significant difference (19). In addition, some of the studies indicated that NLR was associated with severity (4,12,16), outcome (17), and proteinuria (4) of PE.

Currently, four case-control studies investigated the relationship between NLR and PE (15,20–22). Two of these four studies indicated that increased NLR in first (20) and second trimester (22) was a risk factor for PE. But in one study with large sample size (118 PE patients and 1,495 normal pregnant women), the authors failed to found NLR before the twentieth pregnancy week was increased in PE patients (15).

Findings of study done by ***Kang et al., 2020*** shows that NLR represents a promising predictive biomarker, as its significantly elevated in pre eclamptic pregnancies, especially in severe ones (23). However, certain aspects remain to be explored in order to fully elucidate its utility in clinical practice. Further large-scale prospective cohort studies are needed in order to accurately assess the role of NLR in PE. Cases should be discriminated according to the onset and the severity of the disease, as well as the presence of fetal growth restriction. NLR should be sequentially measured throughout pregnancy, to reveal the most appropriate gestational age for sampling. Furthermore, cut-off values should be introduced, in

order to investigate the predictive efficacy of this marker. These values should be pre-determined, eliminating the risk of overestimating the diagnostic performance. Finally, NLR should be evaluated in conjunction with the conventional PE markers and be incorporated in combined models that would offer optimum efficiency in the prediction of the disease.

2. *Neutrophil-Lymphocyte Ratio as a Prognostic Biomarker of Pre-eclampsia:*

Pregnancy have been linked to several parameters such as body mass index (BMI), woman's age, uterine and cervical malformations and lifestyle habits. Pregnancy can also be jeopardized by many complications such as gestational diabetes mellitus, hypertensive disorders of pregnancy and preeclampsia, infectious and several systemic pathological conditions, such as immunological, endocrine, cardiovascular, haematological, metabolic, gastroenterological, oncological and kidney diseases .

Neutrophils to lymphocytes ratio (NLR) when measured in the first trimester of pregnancy, has been associated with pregnancy complications; an increased value has been associated with underlying inflammatory processes. For example, in preeclampsia, and especially in its severe manifestations, NLR has been found to be increased when compared to uncomplicated pregnancies (4), and therefore it was suggested that it can be used as a reliable biomarker for the diagnosis of the disease in the first trimester of pregnancy (20,24).

Increased NLR values have also been detected in women with gestational diabetes mellitus, intrahepatic cholestasis of pregnancy and hyperemesis gravidarum (24).

Apart from pregnancy related complications like pre eclampsia NLR is used as a prognostic biomarker in other diseases like metastatic gall bladder cancer, sepsis, stroke, metabolic syndrome and the latest NLR is used for prognostic biomarker in COVID-19 illness (25).

Studies are being conducted to determine and reinstate NLR as a prognostic tool in hypertensive disorders of pregnancy, especially pre-eclampsia. Also raised NLR

ratio is being widely studied to see its impact on various fetomaternal outcome in pre eclamptic women.

Various other Biomarkers used for Prediction of Pre-eclampsia:

	Plasma Concentrations				
Biochemical Marker	1° tremester	2° tremester	Manifest preeclampsia	Reported combinations for prediction	Altered levels are also correlated with
sflt-1	---			- sEng, PIGF, VEGF, - Ultrasound	---
sEng	---			- sflt-1, PIGF, - Ultrasound	- IUGR - HEELP - SGA
PIGF				- sflt-1, sEng - Ultrasound	- IUGR - Preterm delivery - SGA
PP-13					
P-Selectin				Activin A, sflt-1	---
Cell-free fetal DNA				Inhibin A	- IUGR - polyhydramnios - trisomy 21 - preterm labour
Cell free DNA	---	---		---	- trisomy 21 - trisomy 18 - SGA
ADAM12		---	---		
PTX3				---	- IUGR - birthweight - type-2 diabetes m.
PAPP-A					
Visfatin	---				

Table 1.: Today the use of biomarkers in combination with uterine artery Doppler screening is promising as a potential screening tool.

Since many years, different biophysical and biochemical markers have been investigated, based on pathophysiological observations that have been noted in case of preeclampsia, such as placental dysfunction, a generalized inflammatory response, endothelial dysfunction and activation of the coagulation system.

DISCUSSION:

Regardless of the lack of existing prophylactic and therapeutic means against preeclampsia, the search for noninvasive, blood-borne or urinary biomarkers that could predict the development or assist in the detection of this life-threatening pregnancy disorder is still of utmost importance. The availability of such markers could have decisive impact on the medical management of pregnant women and their child (e.g. refer to a tertiary centre) but also on the health costs associated with this poor medical condition. So, early identification of pregnant women at risk for preeclampsia is a priority to implement preventive measures.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONCLUSION:

PE is a multisystem disorder and the pathogenetic steps of the disease are still unclear. Since the only treatment is delivery, timely prediction and prevention are essential to avoid the fetal and maternal consequences, especially of preterm PE. As a result, there is growing interest in the investigation of the role of novel biomarkers that would contribute in the identification of high-risk pregnant women and would shed light on the pathophysiology of the disorder. The findings of our review suggest that NLR value is higher in PE patients especially in severe ones.

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