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Predictive Value of the Neutrophil to Lymphocyte Ratio (NLR) to Predict the Development of Preeclampsia and Pregnancy Induced Hypertension at 1st Trimester

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Abstract

Introduction: Hypertensive disorder in pregnancy affects 4 to 6 percent of all pregnancies and carries risks for the both baby and the mother. Only a few groups of women who are at high-risk pregnancies are received prophylaxis Aspirin, more than 15 percent of women develop pre-eclampsia with a single minor risk factor. **Methods:** This descriptive cross-sectional study was conducted to compare the 1st trimester NLR value of normotensive, pregnancy induced hypertensive and pre-eclamptic pregnant women. The study was conducted with a sample of 416, antenatal patients who were admitted to ward 25, at Colombo North Teaching Hospital Ragama. Data was collected as separated three groups. NLR value was calculated separately and ANOVA test was used to analyze the 3 categorical data. Post HOC test was done to assess the multiple comparison. **Results:** The prevalence rates of pregnancy induced hypertension and pre-eclampsia among the pregnant women were 8.6% and 5.7%. The mean NLR values of normotensive group was 2.708, pregnancy induced hypertensive group was 2.650 and pre eclamptic group was 3.789. There was a significant difference in NLR value between pre eclamptic group and other two groups with P value of <0.001 (Corresponding 95% upper bound for the CI: −0.7132). There was no significant difference of the NLR vales of normotensive and pregnancy induced hypertensive groups (P value of 0.894). **Conclusion:** The 1st trimester NLR value of pre eclamptic patients significantly increased compared to normotensive women.

Keywords

Pre-Eclampsia, Neutrophil to Lymphocyte Ratio, 1st Trimester

1. Introduction

Pregnancy induced hypertension and Preeclampsia are hypertensive disorders that occur in pregnancy and associate with multisystemic involvement, affecting 4% to 6% of all pregnant women [1]. The incidence of non-proteinuria pregnancy induced hypertension is approximately three times greater than preeclampsia.

Because of concerns about potential complications of pre-eclampsia many women who have a normal outcome of pregnancy require frequent and intensive follow ups and surveillance, up to one-fourth to one-fifth of antenatal admissions are as a direct result of monitoring and managing women with hypertension. Current methods for screening of women who are at risk are poor and the onset and progression of the disease are unpredictable.

Hypertensive disorders increase the risk on the fetus, perinatal mortality is also increased especially with pre-eclampsia. Recent studies conducted in UK show 5% of the still births without congenital anomalies were consequence of hypertensive disorders. Severe intrauterine growth restriction is associated with pre-eclampsia particularly when the pre-eclampsia develops at early stage of the pregnancy and there is placental involvement which can be explained by increased incidents of placental abruption with hypertensive disorders. As the delivery is the only cure, the hypertensive disorders in pregnancy have become most common cause of iatrogenic preterm birth. They account the preterm birth rate 1 in 250 women in their 1st pregnancy will give birth before 34 weeks and 8 to 10% of all preterm birth result of hypertensive disorder [1] [2]. Twenty to 25% of women with hypertensive disorders deliver their babies which are small for gestational age. There is strong evidence linking the size at birth to the health in adulthood, there are known as fetal origins of adult disease. Thus, the small babies born due to hypertensive disorder have health implication in their adult life, including an increased risk of hypertension, heart disease and diabetes, when they become adults and also there are neurological sequelae such as learning disabilities and low IQ [3].

Although several theories were introduced, exact etiology until not clearly identified. It is now widely believed that a cascade of reactions leads to the clinical syndrome of hypertensive disorder in pregnancy. There are several accepted theories to explain the development of hypertensives disorder in pregnancy.

A well-known theory is the inadequate trophoblast invasion, however, this is also seen in pregnancy which is complicated by fetal growth restriction without PIH or pre-eclampsia, demonstrating that the maternal syndrome of pre-eclampsia must be related to additional factors.

Studies have shown that inflammation and immunological response at vascular endothelium in pregnancy give rise to vascular dysfunction and which lead to development of Pregnancy induced hypertension and pre eclampsia [2] [4] [5]. Endothelia call activation via inflammatory mediators explains the widespread manifestation of the disease [6]. Also, they have shown altered expression of inflammatory and immune mediators, such Soluble fms-like tyrosine kinase-1 and

soluble endoglin and Interferon-gamma [7]. These mediators alter the composition of the white blood cells in the peripheral blood stream, especially the Interferon-gamma [2] [4] [5].

The ratio of neutrophils to lymphocytes has been introduced to medical research field recently and proven the validity of it as prognostic marker and predictive marker for several different conditions such as cancer, cardiovascular disease [8] and gestational diabetes mellitus [9].

The neutrophil to lymphocyte ratio (NLR) is a basically marker of subclinical inflammation. It is calculated by dividing the number of neutrophils by the number of lymphocytes, usually from peripheral blood sample. The mean range of healthy non pregnant adult value is 0.78 to 3.53 and there is no validated reference range for the pregnancy up to now. Elevated neutrophils to lymphocytes ratio is a poor prognostic indicator. Few studies were done recently show that it also has a value in predicting pregnancy induced hypertension and preeclampsia [5] [10].

Currently no screening test is available in Sri Lankan setting to predict pregnancy induced hypertension or preeclampsia. Although several studies have introduced various biological marks such as serum level of Placental Growth Factory, Urinary podocytes excretion, Circulatory soluble endoglin, Serum Inhibin A and CRP, none of these biological marker

Neutrophil to Lymphocyte Ratio can be calculated simply using an ordinary Full Blood Count, because of that it is a cost-effective predictive marker. Because Neutrophil to Lymphocyte Ratio is calculated from the routine Full Blood Count done at 1st trimester, there is no need to take additional blood samples and no need to do additional investigations, therefore it is feasible to patients if the Neutrophil to Lymphocyte Ratio will be used as a predictive marker.

Improvements in prediction can allow increased surveillance and possible prophylactic therapies to be targeted. The importance of this study is to establish cost effective and accurate predictor to prevent pre-eclampsia and related adverse outcomes.

2. Methods

Main objective of this study was to assess the association between Neutrophil to Lymphocyte Ratio at first trimester and the development of Hypertensive disorder in pregnancy among the pregnant women who are admitted to Colombo North Teaching Hospital Ragama.

2.1. Study Design, Study Setting, Duration and Study Population of the Study

This was a descriptive cross-sectional study conducted in Colombo North Teaching Hospital Ragama, from September to December 2018 and Pregnant women who admitted to Colombo North Teaching Hospital Ragama, ward 25, after 20 weeks of POA (period of amenorrhea) to control blood pressure and pregnant

women who admitted to deliver their child at term, was selected as study population (Normotensive women were selected to study when they are at term and patients who presented with hypertension were selected to study after 20 weeks of POA).

Patients were excluded from the study if any of followings presented: chronic hypertension, Diabetes mellitus, metabolic syndrome, nephropathy, renal or hepatic dysfunction, left ventricular dysfunction, valvular heart disease, malignancy, abnormal thyroid function, local or systemic infection, any medication that alter the immunity (steroids), autoimmune disease such as lupus erythematosus or antiphospholipid syndrome and leucopenia (<3500/ml).

2.2. Sampling

Sample size calculation was done using Lwanga and Lemeshow formulation [11].

$$\text{Sample size} = Z^2 p \times (1-p) \big/ d^2$$

Z = Z value (confidence interval);

p = percentage picking a choice;

d = desire precision (clinically meaningful difference).

We took the p value as 0.5 because we assume the neutrophil to lymphocyte ratio has been increased 50% in pregnant women who has got hypertensive disorder in pregnancy and the nonresponsive percentage as 5%. According to the above formula and the values the minimal sample size was 403 patients. Consecutive sampling was done until fulfill the required sample size

2.3. Data Collection

All the patients who consented to participate in the study had to undergo a brief history taking to find out the presence of exclusion criteria and the patients were excluded from the study if any of followings presented: chronic hypertension, Diabetes mellitus, metabolic syndrome, nephropathy, renal or hepatic dysfunction, left ventricular dysfunction, valvular heart disease, malignancy, abnormal thyroid function, local or systemic infection, any medications that alter the immunity (e.g. steroids), autoimmune diseases such as lupus erythematosus or antiphospholipid syndrome and leucopenia (<3500/ml).

Selected subjects were divided into 3 categories according to blood pressure and the presence of protein in the urine. Blood pressure was monitored by an Intern House Officers as a part of routine medical examination on admission, in all patients. Blood pressure were monitored in seated position using Analogue Mercury sphygmomanometer, patients who were found to have elevated blood pressure for the first time was reassessed to confirm the diagnosis (two or more consecutive occasions 4 hours apart for the patients who had got marginally elevated blood pressure).

Sample of urine from each patient were checked for protein as a routine ward procedure by nursing officers and midwifery officers using urine reagent strip test. It gives visible colorimetric reaction, when the proteins are absent in urine,

the indicator appears yellow in color. However, as the protein concentration increasing in urine the color progresses through various shades of green and finally to blue. The readings are reported in terms of; negative, trace, 1+, 2+, 3+ and 4+ which are compatible with 30, 100, 300, and 2000 mg/dl from 1+. When the reagent strip result was 1+ or more, urine sample was sent for spot urinary protein: creatinine ratio to confirm the diagnosis of significant proteinuria, the cut-off value is more 30 mg/mmol.

Data was collected separately according to following 3 groups, Group1: normotensive, Group 2: blood pressure more than 140/90 without protein urea, Group3: blood pressure more than 140/90 with significant protein urea. Data were collected into a specially formed data collecting sheets.

2.4. Statistical Analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS) version 22. The continuous variable was presented by mean, standard deviation and confidence interval. Assessments of prevalence were calculated using proportions. ANOVA test was used to analyze the differences among 3 categorical groups of data. Association between Neutrophil to Lymphocyte Ratio with other variables were assessed and significant levels were calculated. Multiple comparisons were done using post HOC test (Tukey HSD) and assessed the significance in between 3 groups. The P value of 0.05 was considered statistically significant in the analysis.

2.5. Ethical Considerations

The research proposal was approved by the Board of Study in Obstetrics & Gynecology, Postgraduate Institute of Medicine, University of Colombo. Ethical clearance was obtained from the Ethics Review Committee Faculty of Medicine, university of Ragama. The data collection was totally anonymous with no name, address or identification numbers. Patient autonomy was respected and informed consent was obtained prior to collection of data. The principal investigator described the importance of the study procedure. Blood pressure measuring and urine sample testing were done as routine management procedures of inward patients rather than research procedures.

3. Results

The results were obtained after analyzing the data which was collected in three different categories (normotensive, pregnancy induced hypertension and pre eclamptic) patients who admitted to ward 25 at Colombo North Teaching Hospital Ragama. A total of 416 patients' data was analyzed.

3.1. Prevalence

1) The prevalence of pregnancy induced hypertension among the pregnant women who were admitted to Colombo North Teaching Hospital Ragama was

8.6 per cent.

2) The prevalence of pre-eclampsia among the pregnant women who were admitted to Colombo North Teaching Hospital Ragama was 5.7 percent (Figure 1).

Sixty per cent of pregnant women who developed hypertensive disorders in pregnancy were primiparous women (36 out of 60), out that 60 per cent of primiparous nearly half of women (16 out of 36) developed or progressed into pre-eclampsia before they delivered their babies. Most of those primiparous didn't have major risk factors.

3.2. Description of Data

The sample sizes were 416 and among them 356 patients were normotensive, 36 patients were diagnosed to have pregnancy induced hypertension and 24 patients were diagnosed to have pre-eclampsia.

The mean value of neutrophil to lymphocyte ratio for the normotensive group was 2.708 with standard deviation was 0.702. The mean of the pregnancy induced hypertensive group was 2.650 and the standard deviation was 0.987. The mean of the pre eclamptic group was 3.789 and the standard deviation was 0.879, see Table 1 and Figure 2.

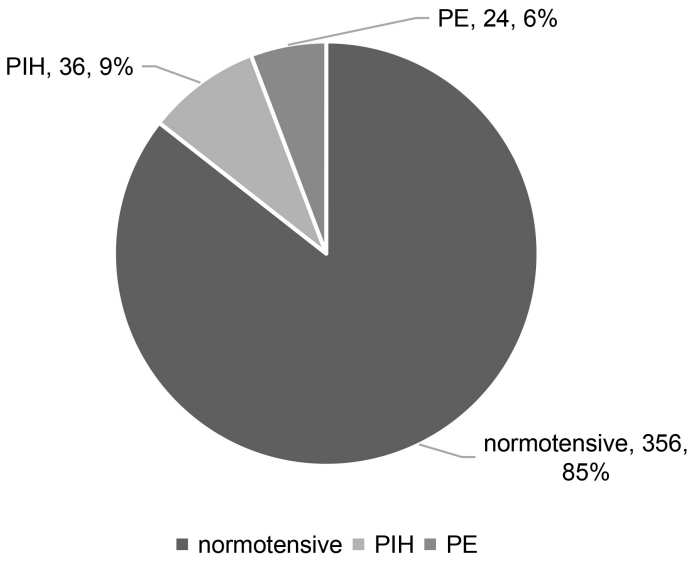

Figure 1. Pie chart of the prevalence of hypertensive disorders in pregnancy at Colombo North Teaching Hospital Ragama.

Table 1. Results of mean NLR values, Standard deviations and sample numbers.

Hypertensive disorders in Pregnancy	Mean of NLR	N	Std. Deviation	Minimum	Maximum
Normotensive	2.7085	356	0.70287	1.12	4.75
PIH	2.6501	36	0.98786	1.62	4.71
PE	3.7898	24	0.87998	2.83	5.93
Total	2.7658	416	0.78258	1.12	5.93

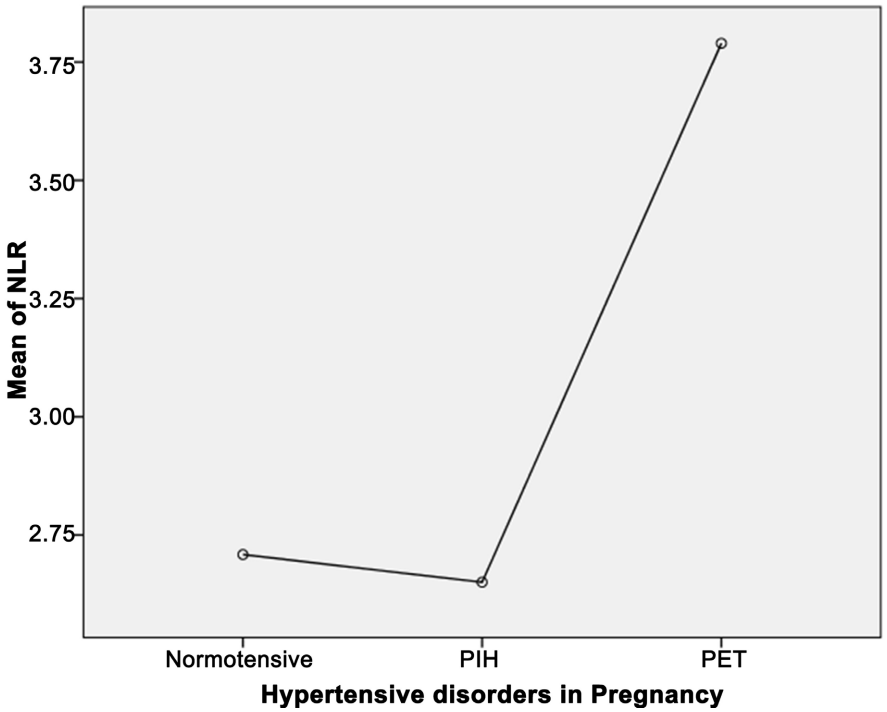

Figure 2. Mean NLR value of Normotensive, PIH and Pre eclamptic groups.

3.3. Analysis of the Significance

The results were analyzed using ANOVA as there were three Categorical data. The null hypothesis was taken as there was no significant difference in all three groups. The analytic result concluded that there was a highly significant difference among the groups and P value was <0.001, see Table 2.

Post HOC analysis

Multiple comparisons were done using post HOC test (Tukey HSD). There was a highly significant difference in between normotensive group and the pre eclamptic group, P value was <0.000 and also a highly significant difference in between pregnancy induced hypertensive group and the pre eclamptic group P value was <0.000. However, there was no significant difference in between pregnancy induced hypertensive group and normotensive group, P value was 0.894, see Table 3.

4. Discussion

4.1. Summary of the Findings

Hypertensive disorder in pregnancy affects 4 to 6 per cent of all pregnancies and carries risks for the both baby and the mother. Only a few groups of women who are at high-risk pregnancies received prophylaxis Aspirin and additional surveillance but more than 15 percent of women develop preeclampsia with a single minor risk factor.

The idea of this study was to introduce a predictive marker to predict hypertensive disorder in pregnancy at early pregnancy which is convenience, simple

Table 2. Results of ANOVA test of NLR values of three categorical data.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	26.813	2	13.407	24.355	0.000
Within Groups	227.343	413	0.550		
Total	254.156	415			

Table 3. Results of multiple comparisons of post HOC teat (Tukey HSD).

Dependent Variable: NLR							
	(I) Hypertensive disorders in Pregnancy	(J) Hypertensive disorders in Pregnancy	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	Normotensive	PIH	0.05838	0.12976	0.894	−0.2468	0.3636
		PE	−1.08123*	0.15647	0.000	−1.4493	−0.7132
	PIH	Normotensive	−0.05838	0.12976	0.894	−0.3636	0.2468
		PE	−1.13961*	0.19552	0.000	−1.5995	−0.6797
	PE	Normotensive	1.08123*	0.15647	0.000	0.7132	1.4493
		PIH	1.13961*	0.19552	0.000	0.6797	1.5995

*The mean difference is significant at the 0.05 level.

and cost effective. At the moment several studies have introduced various biological predictive markers and none of them are available in Sri Lankan setting to predict pregnancy induced hypertension or preeclampsia. This study also looks into the fact that the Neutrophil to Lymphocyte Ratio (NLR) can be calculated from 1st trimester routine basic investigation (full blood count) without doing additional investigations.

The study design was a descriptive cross-sectional study rather than a case control study due to unavailability of validated NLR value for pregnancy in Sri Lankan population. Because the blood components are changed in the pregnancy and also there may be difference due to epidemiological factors. According to the literature review previous studies were done as case control studies. The study was conducted from September to December in 2018 at ward 25, Colombo North Teaching Hospital Ragama. Consecutive sample was selected from the pregnant women who fulfilled the inclusion and exclusion criteria. The total sample size was 416 out of that 85.5 per cent (n-356) were normotensive, 8.6 per cent (n-36) were pregnancy induced hypertensive and 5.7 per cent (n-24) were pre eclamptic.

The prevalence of the hypertensive disorders in pregnancy was 14.4 per cent. The prevalence values were much high compared to worldwide prevalence value which is in between 4 to 6 percent. The reasons for higher prevalence values in this study may be due to the sample size and the study setting. The study was conducted at a tertiary center where the more referrals are received from other hospitals, patients with hypertensive disorders in pregnancy with complications

and specially women who need further care for their affected fetuses. If the study would be conducted in multicenter with larger sample size the prevalence value would be the same as the worldwide value.

The mean value of neutrophil to lymphocyte ratio for the normotensive group was 2.708, the mean of the pregnancy induced hypertensive group was 2.650 and the mean of the pre eclamptic group was 3.789. The mean value of NLR in pre eclamptic group was significantly higher compare to both normotensive and PIH group with a corresponding P value of 0.000 (corresponding 95% CI).

This study concluded that the 1st trimester NLR value of the pre eclamptic group of patients were significantly higher than other two groups and the NLR value has been changed from the beginning of the pregnancy before the patient develop signs and symptoms and specially before they fulfill the diagnostic criteria of "after 20 weeks of pregnancy". Because of that NLR can be introduced as a feasible and cost-effective predictive marker to find out patient who are at risk to developed pre-eclampsia.

4.2. Importance and Implications of the Findings

Sri Lanka is a developing country and which provides free health care service at field and hospital setting. Although there are multiple predictive makers that were introduced at research level to detect patients who are at high risk to develop hypertensive disorders in pregnancy, most of those predictive markers are not available at government hospital setting and none of those predictive markers are feasible or cost effective.

At the moment in our antenatal clinics patients are offered universal screening for gestational diabetes mellitus (GDM), as gestational diabetes mellitus, it is important to screen high risk women for hypertensive disorders in pregnancy because it has high complication profile for the pregnant women and their babies. However, there is no good screening tool to detect high risk group expect the clinical risk assessment.

Most of the women who are followed up at antenatal clinics, under go full blood count routinely in 1st trimester to assess the hemoglobin (Hb) level rather than the Hb level only. Because of that NLR can be calculated without any more blood sampling and spending extra expenditure.

NLR is a simple ratio which can be calculated simply by dividing the neutrophil count by lymphocyte count.

According to the results of this study the NLR value can be used at 1st trimester to detect pregnant women who are at risk to develop pre-eclampsia with no other major risk factors suggested by clinical history. More than 15 per cent of women develop pre-eclampsia with a single minor risk factor.

Current NICE guideline suggests to start aspirin at 12 weeks of POA to prevent pre-eclampsia in women who are at high risk and the prophylactic aspirin should be started before the 16 weeks of POA to receive the benefits prevention and minimize the both maternal and fetal complication. They have also sug-

gested 5 major risk factors and 6 minor risk factors, aspirin should be started in patient who are presented with one major risk factor or presence of more than two minor risk factors. All those risk factors can be detected by taking detail clinical history and go through the previous medical records. However, as I mentioned above, more than 15 per cent of women develop pre-eclampsia with a single minor risk factor and most of them are primiparous women and they don't receive antenatal aspirin prophylaxis, by the time they develop signs and symptoms they have exceed the 16weeks of POA.

As NLR value of the 1st trimester significantly associated with later developing pre-eclampsia, it can be easily implicated to medical practice at antenatal clinic setting to detect that group of women who are at high risk and they can't be simply detected by clinical risk assessment and they can be prescribed Aspirin to prevent development of pre-eclampsia and minimizes its complications.

Predictive value of the NRL can be suggested to make more focus on high-risk group of patients who are presented with major or minor risk factors and Aspirin prophylaxis can be prescribed in more focus manner as at the moment the number needed to treat in order to prevent pre-eclampsia is 114 and to prevent one serious adverse outcome is 51.

5. Limitations and Validity of the Study

5.1. Methodology and Statistical Analysis

Originally in the research proposal the only inclusion criteria was patients who has under gone full blood count at latter part of the 1st trimester (at the gestation from 8 to 12 weeks) and which should be done only from the laboratory of the Colombo North Teaching Hospital Ragama. However, in the research setting it was very difficult to include the patients who has got hospital laboratory reports. Even the patients who were followed from the beginning at Ragama hospital done their investigations outside. In addition to our hospital clinic patients, most of the pregnant women with pre-eclampsia were referred from other antenatal clinics and other stations and they had done they investigations in separate laboratories thereby the inclusion criteria were changed to accept reports from various laboratories. Since this difference affects all three categorical groups it is unlikely that it has an effect on the final outcome of the study.

Other than for the above-mentioned amendments there were no major issues with carrying out the study in keeping with the proposed methodology.

5.2. Internal Validity

Effects of the confounding factors such as prophylaxis aspirin on the final outcome, it is an evidence base fact that aspirin prevents the occurrence of pre-eclampsia. Usually, aspirin is started at 12 weeks of POA and which is after the 1st trimester routine full blood count blood sampling. In the study sample, there were few patients in every categorical group who were on prophylactic antenatal aspirin. All patients who had major risk factors which were suggested by NICE

guideline to recommend prophylactic aspirin were exclude from the study as those conditions can alter the NLR value prior to the pregnancy. However, there were few patients who were on aspirin which was started because of the presence of minor risk factors and other reasons such as previous poor pregnancy outcome (Recurrent pregnancy losses, fetal growth restriction).

Presence of local or systemic infection can alter the NLR value. Although there was an exclusion criterion to exclude those patients who had local or systemic infection at the time of sample collection, it was very difficult to patient to recall that as the data were collected several months after that event.

5.3. External Validity

This study was conducted at ward 25, Colombo North Teaching Hospital Ragama which is a tertiary center and the data were collected within limited time frame and with minimum required sample size. In this study we found that higher prevalence rates of pregnancy induced hypertension and pre-eclampsia. Generalization of the prevalence values will be remarkably affected by these factors.

This study was conducted to evaluate predictive value of the neutrophil to lymphocyte ratio to predict the development of pre-eclampsia and pregnancy induced hypertension at 1st trimester. Although there is no validated screening test to find out the risk group, worldwide and elsewhere in the country practice risk assessment and prophylactic Aspirin on high-risk group as suggested by NICE guideline to prevent pre-eclampsia and its complications.

6. Conclusion and Recommendations

6.1. Conclusion

First trimester Neutrophil to Lymphocyte ratio of the pre eclamptic patients were significantly higher compared to normotensive pregnant women. Therefore, NLR value of the 1st trimester can be used to predict the development of pre-eclampsia.

There are no significant changes in NLR value of the pregnancy induced hypertensive patients compared to normotensive pregnant women. Therefore, NLR value of the 1st trimester cannot be used to predict the development of pregnancy induced hypertension.

6.2. Recommendations

Neutrophil to Lymphocyte ratio can be introduced as a simple and cost-effective predictive marker to predict the development of pre-eclampsia, for that further study should be carried out to validate the NLR value and make cut-off values for the normal pregnancy and the cut-off values to predict the development of pre-eclampsia.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

NLR—Neutrophil to Lymphocyte Ratio;
PIH—Pregnancy induced hypertension;
PE—Pre eclampsia;
P value—Probability value;
CI—Confidence interval;
POA—Period of amenorrhea;
NICE—National Institute of Health Care Excellence.