Research article

Role of neutrophil to lymphocyte ratio at booking visit in prediction of gestational diabetes

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Abstract

Introduction: Gestational Diabetes Mellitus (GDM) affect up to approximately 10% of all pregnancies. Various markers of inflammation have been shown to predict the future diabetes risk and Neutrophil Lymphocyte Ratio (NLR) level is significantly correlated with metabolic syndrome criteria. However, very few studies investigated any possible association between NLR and development of GDM.

Objectives

- To compare the NLR among GDM group and control group.
- To identify an optimal cut-off value of NLR in predicting GDM.

Methods: A longitudinal observational study in all pregnant women who are in their first trimester at antenatal clinic, Teaching Hospital, Kandy for six months was carried out with a Full Blood Count at the first trimester and Oral Glucose Tolerance Test (OGTT) at the 24-28 weeks of gestation. Sample size was 361 and non-probability convenient sampling technique was applied.

Results: Mean NLR value was 3.16 (SD=1.84) and the difference between GDM and non GDM mothers was not significant. Left upper most value for NLR of the ROC curve is 1.32 and when it is used as the cut off value the sensitivity is 99.6% and the specificity is 21.2%.

Conclusions and recommendations: NLR positively correlates with the OGTT values done at 24-28 weeks of gestation, which can be used as a predictor at early booking visit. There is no significant difference between the mean value of participants with or without GDM. Prediction of GDM by NLR should be further studied in a well-targeted study population with wide methodology.

Key words: gestational diabetes, neutrophil lymphocyte rati

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Introduction

Gestational diabetes mellitus (GDM) is defined classically as carbohydrate intolerance resulting hyperglycemia with variable severity which onset or first recognition during pregnancy[1]. It creates a significant risk for both mother and the fetus during antenatal, intrapartum and post natal periods[2].

Even though global prevalence of GDM is 2-6%, it may reach 10-20% in high-risk populations, with an increasing trend across most racial/ethnic groups studied[3]. According to the world diabetes report published by the WHO in 2016, second highest prevalence of GDM is reported among the south East Asian countries including Sri Lanka[4]. Prevalence of GDM in Sri Lanka, in year 2014 was 18%[5] in 2016 prevalence of GDM in urban and suburban areas of Sri Lanka was reported as 13.8%[6].

The probability of gestational diabetes for a woman who has had gestational diabetes in a previous pregnancy is 30-84% and recurrence of gestational diabetes in women with insulin-treated gestational diabetes in a previous pregnancy is approximately 75% and therefore it is clearly evident that early diagnosis of GDM is essential for early intervention and management[7].

The 'gold standard' diagnostic test for gestational diabetes is the 75 g oral glucose tolerance test (OGTT) conducted at 24-28 weeks of gestation[8]. Oral Glucose Tolerance Test (OGTT) is a relatively unpopular diagnostic test, with practical difficulties. As it requires intake of a high concentrated glucose solution and several blood drawing episodes, pregnant mothers generally dislike the OGTT[9]. On the other hand an additional burden is created on the health care staff as it requires drawing of several blood samples with regular intervals and analysing them. Therefore world attention is focussed on methods to minimize the number of pregnancies which demand OGTT[10,11]. Requirement of OGTT can be minimized by screening procedures with high predictability around the world special attention is aimed at experimenting more feasible cost effective and cheap screening procedures concerning gestational diabetes mellitus and type II diabetes mellitus.

Sex hormone binding globulin (SHBG), C-reactive protein (CRP), adiponectin, galanin, maternal serum levels of placental growth factor, glycosylated fibronectin level, Neutrophil to lymphocyte ratio (NLR) has showed promising results but further studies with reasonable amount of sample size are recommended to confirm the findings[12].

NLR provides a simple method for assessment of inflammatory status and it is a new, inexpensive marker where the differential counts of each component considered[13]. Since inflammation plays a central role in the pathophysiology of obesity, diabetes mellitus and cardiovascular complications, role of NLR in these conditions has been studied[13]. However very few studies investigated any possible association between NLR and development of GDM. First study, published in 2014 considering 42 women with GDM and 68 women without GDM showed elevated levels of NLR in GDM group[13]. Their Full Blood Count was followed by a diagnostic 4-point 100-g-OGTT within 2 weeks and GDM was diagnosed by the Carpenter and Coustan criteria[15]. The data showed significantly high NLR in GDM women (3.00±0.83 vs. 2.26±0.43 $p<0.001$). The study calculated that more than 2.93 of NLR has the ability to predict GDM with 94.1% specificity and 76.2% sensitivity.

The aim of the present study was to investigate the predictive value of NLR on development of GDM in view of utilizing it to apply life style, dietary modifications from first trimester to prevent GDM and consider it as an individual risk factor to perform early OGGT in higher risk population. Also it would be an readily available biomarker to predict GDM as most of the pregnant women in Sri Lanka undergo a FBC in their booking visit to detect their haemoglobin levels[14].

Methodology

This Longitudinal observation study was conducted at the Antenatal Clinic, Teaching Hospital Kandy from June 2016 to December 2016. Lwanga and Lemeshow equation[15] was used for the sample size calculation. According to previous study findings prevalence of GDM in Sri Lankan population was 18%[5]. Expected sensitivity for this study was 75% and expected specificity was 95%. Three hundred sixty one pregnant women recruited using non-probability convenient sampling technique in to cases (n=288) and controls (n=73). Inclusion criteria for the study was Singleton pregnancies who presented before 12 weeks of gestation.

Women with ongoing acute and chronic infections, chronic inflammatory conditions, WBC > 12000/µl,

WBC<3500/µl, habit of smoking, established diabetes and other metabolic diseases were excluded. Even though WBC rises physiologically in pregnancy it is mainly marked from 2nd trimester onwards. Therefore normal adult cut off values used as exclusion criteria in this study.

Eligible mothers who fulfilled the entry criteria were consented with informed written consent and investigator administered data collection sheet was used as the study instrument.

All the subjects who participated in the study performed their routine booking visit full blood count test in Teaching Hospital Kandy laboratory. All the blood samples were analysed in same machine and differential counts were done manually by one technician to avoid machine dependent errors. All the test results were collected by author himself and privacy of the results were maintained strictly. All the subjects did their OGTT (26 to 28 weeks of gestation) at Teaching Hospital Kandy and analysed in same machine. According to International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations, subjects with positive OGTT (FBS>/ 92 mg/dl,1 hour plasma glucose > 180 mg/dl, 1 hour plasma glucose > 153 mg/dl and one value out of three is sufficient) were considered as GDM[2].

SPSS version 23.0 was used for all the calculations. Mean and standard deviation were used to describe continuous variables and chi squire test was used to describe categorical variables. 0.05% probability cut-off and 95% confidence interval were applied for statistical significance. Receiver Operating Characteristic (ROC) curve was applied to predict the diagnostic test accuracy. Left upper most value of the ROC curve was taken as optimum cut-off value for particular exposure variable which could be achieved satisfactory sensitivity and specificity.

Results

Table 1 shows basic demographic characteristics (the distribution of age, parity and BMI value) among the study participants. Age of the participants ranged from 20 years to 43 years (Mean: 31.29, SD: 4.88). Majority represents the 26-35 years age group (N=239:66.7%), and majority of the study participants were primi mothers (38.8%; N=139) BMI value of the study participants ranged from 16.02 to 33.77 (Mean 24.78; SD3.01). Majority were included into the 19.1-24.9 group.

Table 1. Distribution of age, parity and BMI among participants

Parameter		Number (N)		Percentage (%)	
Age		GDM	Non GDM		
	<25	15	28	11.7	
	26-30	83	25	30.1	X^2=50.89
	31-35	116	15	36.6	df=3
	>36	69	10	21.6	P<0.001
Parity					
	1	110	29	38.8	
	2	85	20	29.2	X^2=174.02
	3	66	20	23.5	df=4
	4	17	03	55	P<0.001
	5	10	01	3.0	
BMI					
	<19	01	13	3.8	
	19.1-24.9	130	40	47.3	X^2=273.1
	25-29.9	151	15	45.9	df=3
	>30	06	05	3.0	P<0.001
Total	288	73	100		

Main exposure variables of the present study were the WBC counts and their ratios. Minimum recorded WBC count of the study participants was 6.4×10^3 and the maximum recorded WBC count was 12×10^3 (Mean =10.37: SD=1.54). Percentage of the neutrophils varied from 47% to 88% (Men 67.63: SD.7.76). Lymphocyte value changed from 51% to 89%. Haemoglobin values of the whole study sample were in an acceptable range and the minimum value was 10 g/dl (Mean=12.9: SD=1.09). Neutrophils to lymphocyte ratio ranged from 0.921 to 9.83 (Mean=3.16: SD =1.841).

Table 3 depicts the degree of correlation of selected variables with the neutrophil lymphocyte ratio. Fasting blood sugar value at the 28 weeks of gestation was positively correlated with neutrophil lymphocyte ratio (r=0.25). Oral glucose tolerance value at the first hour after the meal was positively correlated with the first trimester neutrophil lymphocyte ratio (r=0.219) and second hour oral glucose tolerance value was negatively correlated with the neutrophil lymphocyte ratio (r=-0.153).

Above ROC curve describes the correlation of NLR value to predict the occurrence of GDM during the last trimester of pregnancy. X axis shows the false positive rate and Y axis indicates the true positive rate. Almost the whole ROC curve lies below the diagonal line and the area under the curve is 0.457 (SE: 0.038: p<0.241). Therefore when a participant with GDM at 28 weeks is predicted by NLR at booking with 45.7% accuracy. When achieving the highest sensitivity NLR value is 1.31 and when achieving the highest specificity NLR value is 4.41. Left upper most value of NLR in the ROC curve is 1.32, and when thatvalue is used as the cut off value the sensitivity value is 99.6% and the specificity value is 21.2%.

Table 2. Distribution of white blood cells among study participants

Parameter	Min	Max	Mean	SD
WBC	6.4	12	10.37	1.54
Neutrophil %	47	88.5	67.63	7.76
Lymphocyte %	89	51.0	25.64	8.69
Haemoglobin	10.0	14.3	12.09	1.09
NLR	0.921	9.83	3.161	1.841

Table 3. Distribution of correlation between selected variables

Parameter combination	r	95% Confidence Interval
NLR-FBS	0.25	0.133-0.164
NLR-OGTT 1st hr	0.219	0.087-0.334
NLR-OGTT 2nd hr	-0.153	-0.224-0.083

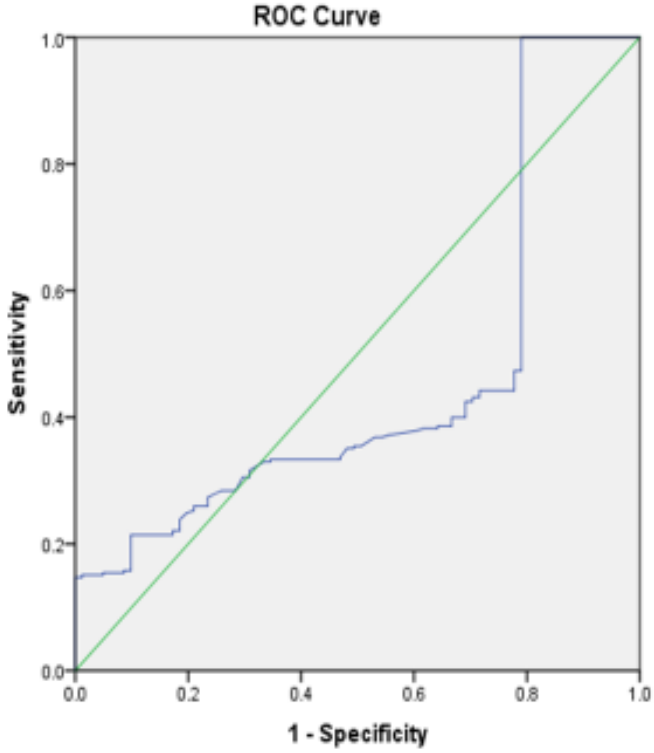

Figure 1. **Distribution of ROC curve – gestational diabetes mellitus with neutrophil lymphocyte ratio.**

Discussion

Current study and the study conducted by Yilmal et al both clearly demonstrates women with GDM were older, higher BMI and with a family history of GDM than Non-GDM women[13]. Both studies shows positive correlation of NLR with GDM[13]. In our study Mean NLR value was 3.16 (SD=1.84) and the difference between GDM and non GDM mothers was not significant. In contrast previous study showed significantly high NLR in GDM women (3.00±0.83 vs. 2.26±0.43 $p<0.001$). While the previous study gave an optimum cut off value for NLR of 2.93 (sensitivity – 76.2, specificity – 94.1) and the current study shows cut off value of 1.32 (sensitivity – 99.6, specificity – 21.2)[13]. Major difference between current study with previous study was current study assessed NLR in booking visit and previous study analysed NLR from blood sample drawn at the same time of routine OGTT between 24-28 weeks of gestation[13]. Therefore this is the first study, which showed positive correlation of NLR at booking visit with development of GDM later in pregnancy to our best knowledge. In Sri Lanka full blood count is routinely ordered in booking visit to assess the haemoglobin level of every women. Therefore parameters of other blood cells become freely available and calculation of NLR does not require any additional expenses or interventions. This is considered as an additional benefit and a procedure with a higher cost effectiveness.

There were some limitations of this study. When study sample was selected it was limited to a single study setting and a non-probability convenient sampling technique was used. Therefore the representativeness of this study sample is not ideal. Also results were dependent on single occasion instead of serial measurements, so laboratory measurement errors may affect the accuracy of data.

Conclusion and recommendations

Neutrophil lymphocyte ratio at 1st trimester positively correlates with OGTT values done at 24-28 weeks of gestation with considerable potential to use as an early predictor of occurring GDM. However prediction of it should be further studied in wider methodology, using well targeted study population

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