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# Circulating Potassium/Magnesium Ratio, Thyroid Stimulating Hormone, Fasting Plasma Glucose, Oxidized LDL/Albumin Ratio, and Urinary Iodine Concentration Possible Entities for Screening for Preeclampsia in Low-Resource Settings

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Article

# Circulating Potassium/Magnesium Ratio, Thyroid Stimulating Hormone, Fasting Plasma Glucose, Oxidized LDL/Albumin Ratio, and Urinary Iodine Concentration Possible Entities for Screening for Preeclampsia in Low-Resource Settings

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## Highlights

### What are the main findings?

- This study found that some routine analytes at optimum thresholds were associated with preeclampsia
- Serum potassium/magnesium ratio and urinary iodine concentration had the highest sensitivity and specificity.

### What is the implication of the main finding?

- There is a need for further evaluation of these potential biomarkers for screening for preeclampsia in low-resource settings and populations at risk of micronutrient deficiency in pregnancy

**Abstract:** Background and Objectives: Several micro and macronutrient malnutrition states that are routinely assessed during clinical care of women in the antenatal period have been proposed as risk factors for preeclampsia. However, there is a paucity of data on the potential use of these biomarkers for detection of preeclampsia. The aim of this case-control study was to investigate the association of biomarkers from routine clinical tests, and those specific to micro and macronutrient malnutrition, with the risk of preeclampsia. Materials and Methods: Venous blood samples of 250 participants with preeclampsia and 150 pregnant women without preeclampsia were collected and assayed immediately for the full blood count, urea and electrolytes, high-density cholesterol (HDL), total cholesterol, triglycerides, low-density lipoprotein (LDL), oxidized low-density lipoprotein (OxLDL), selenium in addition to Urine iodine concentration (UIC). Results: The serum potassium/magnesium ratio (K<sup>+</sup>/Mg<sup>2+</sup>), UIC, fasting plasma glucose (FPG), thyroid stimulating hormone (TSH), lymphocyte percentage (L/WBC%) and the oxidized LDL/albumin ratio (OxLDL/Alb) were identified as independent predictors of preeclampsia. Conclusion: Serum Potassium/Magnesium ratio and other analytes, some of which are easily acquired in routine practice, and reflecting various biological processes, had good performance at predicting prevalent preeclampsia.

**Keywords:** preeclampsia; prediction; biomarkers; potassium/magnesium ratio; urinary iodine excretion; FPG; TSH

## 1. Introduction

Preeclampsia complicates 3 to 8% of all pregnancies and is one of the major causes of perinatal mortality and morbidity [1]. In the long term, it also accounts for an increased risk of premature cardiovascular diseases in both mothers and their offspring, secondary to structural modification of proteins, lipids and epigenetic changes that affect DNA expression. Several risk factors for preeclampsia have been identified. These include a maternal or family history of preeclampsia or hypertension, ethnicity, extremes maternal age, primiparity, primipaternity, in-vitro fecundation (IVF), multiple pregnancy, obesity, and systemic disorders such as diabetes mellitus (DM), kidney disease, autoimmune diseases [1]. In an attempt to identify women at high risk of preeclampsia, several biomarkers have been studied. These include serum and plasma markers of placental function, endothelial dysfunction, renal dysfunction, general metabolic status, oxidative stress, and haemolysis and inflammation. However, most biomarkers have yielded low sensitivity and specificity for the prediction of preeclampsia [2–4]. So far, the main predictive markers are those that are associated with placental function which include the placental growth factor (PlGF), and soluble Fms-like tyrosine kinase 1 (sFlt-1) [2–5]. The PlGF has been found to identify women at risk of preeclampsia from as early as 11 weeks of amenorrhoea (WOA) while the sFlt-1 is more predictive of preeclampsia among women with gestation age  $\geq 20$  WOA [6–13].

Studies from central Africa showed that both micronutrient (selenium and iodine deficiency) and macronutrient malnutrition (obesity) were risk factors for preeclampsia [14,15]. This retrospective case-control study was conducted to investigate the biomarkers from routine blood tests and those specific to micro and macronutrient nutrition that are associated with the risk of preeclampsia [16].

## 2. Materials and Methods

### 2.1. Study Design

This study was carried out as a secondary analysis of archived data (case-control study design) of pregnant women who were part of the Communicable Disease, Nutritional, Environmental Epidemiology and Cardio-metabolic Risk Study conducted in Kinshasa Province, Democratic Republic of Congo between 2007 and 2008 at Lomo Medical Centre, Kinshasa Limete.

### 2.2. Study Population

One hundred and fifty normotensive pregnant women at term were enrolled in the Communicable Disease, Nutritional, Environmental Epidemiology, and Cardio-metabolic Risk Study upon diagnosis and matched for age and parity with three hundred participants with preeclampsia 150 controls (a ratio of 1 control: 2 cases). However, 50 participants were excluded from the current study due to incomplete data.

### 2.3. Methods

Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy [17] Participants were diagnosed with pre-eclampsia when they presented with new onset of hypertension ( $>140$  mmHg systolic (SBP) and or  $>90$  mmHg diastolic (DBP) blood pressure) after 20 weeks gestation with proteinuria (spot urine protein/creatinine  $>30$  mg/ mmol, or  $>300$  mg/day or 2+ on dipstick testing) or other maternal organ dysfunction: renal insufficiency (creatinine  $>90$   $\mu\text{mol/L}$ ;  $1.02$  mg/dL); liver involvement (elevated transaminases – at least twice upper limit of normal  $\pm$  right upper quadrant or epigastric abdominal pain), neurological complications (altered mental status, blindness, stroke, hyperreflexia, severe headaches, and persistent visual scotomata), haematological complications (thrombocytopenia – platelet count below  $150,000/\text{dL}$ , disseminated intravascular coagulation or haemolysis) and uteroplacental dysfunction (foetal growth restriction, abruptio placentae or intrauterine foetal death). Participants were diagnosed with severe pre-

eclampsia when they presented with SBP >160 mmHg or DBP >110 mmHg with or without systemic organ involvement. Participants were diagnosed with eclampsia when they presented with SBP >140 mmHg or DBP >90 mmHg after 20 weeks gestation accompanied by convulsions.

Trained nurses measured height, weight, waist circumference (WC), SBP and DBP to standardized procedures. Blood pressure was measured according to the American Heart Association guidelines, with the patient's elbow flexed at the heart level. The average of the two measurements with a standard mercury sphygmomanometer taken at intervals  $\geq 2$  minutes after the participants had been sitting for at least 30 minutes was used [18].

Venous blood was collected from the cubital fossa between 7:00 and 9:00 a.m. into ethylenediaminetetraacetic acid (EDTA) and sodium fluoride (NaF) vacutainers. The samples were processed and assayed immediately to measure the full blood count (FBC), Urea and electrolytes (U&E), the concentrations of high-density cholesterol (HDL), total cholesterol, triglycerides, low-density lipoprotein (LDL), oxidised low-density lipoprotein (oxLDL), C-peptide, and glucose. Laboratory data were obtained using calibrated and standard routine procedures and specific protocols of the manufacturers' such as CyFlowR Counter (Partec GmbH, Munster, Germany), Hydrasys system, Serbia, Evry, France), spectrophotometer Hospital Diagnostics (Florence, Italy), kits of Biome'rieux (Marcy l'Etoile, France) and Mercodia AB (Silveniusgatan 8 A, SE754, Uppsala, Sweden, and a caloric Sensor Hach DR/2010 spectrophotometer (HACH, USA). TSH was measured by enzyme-linked immunosorbent assay method purchased from DIALAB GmbH IZ-NOE Sued Company, Hondastrasse, Objekt M55, A- 2351 wr, Neudorf, Austria. NO was measured using Cayman kits (Cayman Chemical Company Ann Arbor, MI). Urinary iodine concentration was measured using the Sandell-Kolthof method.

Variables studied as possible predictors of preeclampsia included morphological markers such as waist circumference (WC) and hip circumference (HC) for metabolic syndrome (MS), systolic and diastolic blood pressure, while laboratory data were circulating markers or biomarkers associated with metabolic syndrome which included: triglycerides, total cholesterol, HDL, LDL, glucose, and uric acid; NO for endothelial dysfunction; Vitamin C for exogenous anti-oxidants; Lymphocytes percent, serum ferritin, anti-Helicobacter pylori IgG, GGT and CRP for inflammation, infections, and cytokines; Selenium deficiency a key trace element in nutrition and oxLDL for oxidative stress imbalance and atherosclerosis; Cortisol for distress hormone; UIC and TSH for iodine nutrition and thyroid hormones.

#### 2.4. Statistical Analysis

Proportions of categorical variables were compared using the chi-square test, while means of continuous variables were compared using Student's *t*-test or ANOVA. The Kruskal-The Wallis test was used to compare the medians of non-normally distributed data. A *p*-value of < 0.05 was considered statistically significant. Logistic regression was carried out to identify the biomarkers that can act as independent predictors of preeclampsia in the study population. The diagnostic performance of these biomarkers at discriminating preeclamptic participants and normotensive controls was tested using the receiver operating characteristic curve (ROC). The areas under the curve (AUC) with the corresponding 95% confidence intervals, the Standard error, and the sensitivity and specificity at the optimal cut-off values of the candidate diagnostic biomarkers were calculated. These optimal cut-offs were derived using the Youden index method. All analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 23.0 (SPSS Inc) Chicago, IL, USA.

### 3. Results

#### 3.1. General Characteristics

The median (IQR) age was 33 (29 – 37.5) years for cases and 33.5 (33.5 – 37) years for controls, *p* = 0.135. The median (IQR) gestational age (weeks of amenorrhea) at recruitment and sample collection was 32 (24 – 37.5) for cases and 39 (38 – 39) for controls, *p* <0.001.

### 3.2. Biomarkers Associated with Preeclampsia

Table 1 summarizes the median (25th and 75th percentile) serum values of several biomarkers of cases and controls. This univariate analysis showed higher levels ( $p < 0.05$ ) of low-density cholesterol (LDL), oxidized low-density cholesterol (OxLDL), triglycerides (TG), total cholesterol (TC), waist circumference (WC), hip circumference (HC), body mass index (BMI), fasting plasma glucose (FPG), cortisol, TSH, T3, T4, OxLDL /Albumin ratio,  $\gamma$ -glutamyl transferase (GGT), C-reactive protein (CRP), potassium/magnesium ratio among cases of preeclampsia than controls.

**Table 1.** Median (25th and 75th percentiles) levels of various analytes of cases and controls.

Biomarker	Cases	Controls	P
	Median (25p, 75p)	Median (25p, 75p)	
HDL -C mg/dL	16.0 (12.0, 29.6)	21.5 (12.0, 45.8)	0.080
LDL -C mg/dL	125.0 (87.0, 154.0)	121.0 (67.0, 134.0)	0.003
Oxidised LDL IU/L	167.0 (89.0, 221.0)	82.0 (19.7, 212)	<0.0001
Triglycerides mg/dL	144.5 (84.0, 189.0)	84.0 [67.8, 139.5)	<0.0001
Total Cholesterol mg/dL	145.0 (125.0, 199.0)	126.0 (95.3, 145.2)	<0.0001
Waist Circumference cm	79.0 (72.0, 90.0)	75.0 (70.0, 79.0)	<0.0001
Hip circumference cm	98.0 (87.0, 104.0)	92.0 (85, 97.3)	0.001
BMI Kg/M <sup>2</sup>	24.6 (20.8, 28.0)	21.8 (19.0, 25.8)	<0.0001
FPG mg/dL	116.0 (99.0, 180.0)	103.0 (89.0, 125.7)	<0.0001
Cortisol nmol/L	32.9 (18.0, 54.0)	18.0 (18.0, 32.0)	<0.0001
Vitamin C mg/dL	0.45 (0.21, 2.0)	0.60 (0.22, 5.0)	0.002
Selenium $\mu$ g/L	9.0 (9.0, 17.3)	44.0 (21.0, 102.7)	<0.0001
UIC $\mu$ g/L	90.0 (78.0, 157.2)	351.0 (299.0, 555.0)	<0.0001
TSH mIU/L	6.3 (4.1, 8.0)	2.5 (0.13, 4.4)	<0.0001
T3 ng/mL	1.32 (1.16, 1.68)	1.16 (1.0, 1.36)	<0.0001
T4 $\mu$ g/dL	10.9 (9.3, 12.4)	9.8 (8.4, 11.5)	<0.0001
NO $\mu$ mo/L	2.0 (1.0, 6.0)	20.9 (4.0, 43.3)	<0.0001
Oxid LDL/ Alb ratio	13.0 (9.0, 16.0)	3.6 (2.0, 12)	<0.0001
Serum Ferritin ng/mL	213.0 (180.0, 345.0)	199.0 (167.0, 340.0)	0.114
GGT U/L	99.0 (88.0, 113.0)	33.0 (11.0, 99.0)	<0.0001
CRP mg/dL	58.5 (39.0, 66.0)	57.0 (12.0, 88.0)	0.024
Lymphocyte %	22.0 (16.0, 25.6)	26.5 (23.5, 38.5)	<0.0001
Serum K <sup>+</sup> mmol/L	3.6 (2.8, 6.0)	4.0 (3.8, 4.0)	0.149
Serum Mg <sup>2+</sup> mmol/L	0.12 (0.09, 0.19)	0.97 (0.76, 1.0)	<0.0001
K <sup>+</sup> /Mg <sup>2+</sup> ratio	28.5 (17.3, 44.3)	4.1 (3.7, 5.3)	<0.0001

OxLDL/Alb Ratio: Serum Oxidized LDL cholesterol/Albumin ratio; UIC: urine iodine concentration; FPG: Fasting Plasma Glucose; K<sup>+</sup>/Mg<sup>2+</sup>: Serum Potassium/Magnesium ratio; TSH: Thyroid stimulating hormone.

The levels of vitamin C, selenium, nitric oxide (NO), lymphocytes, serum magnesium and urinary iodine concentration (UIC), were lower ( $p < 0.05$ ) among cases of preeclampsia than controls. However, the serum HDL and potassium levels were not significantly different ( $p \geq 0.05$ ) between cases of preeclampsia and normotensive controls.

### 3.3. Independent Predictors of Preeclampsia

All biomarkers that were significantly associated with preeclampsia on univariate analysis were entered a the binary logistic model. After adjustment for confounding factors (all variables not maintained in the equation), only the oxLDL/albumin ratio, lymphocyte percentage, UIC, K<sup>+</sup>/Mg<sup>2+</sup> ratio, TSH and FPG were identified as significant predictors of preeclampsia (Table 2).

**Table 2.** Analytes that independently predicted the occurrence of preeclampsia in the study population.

Variable	B	S.E.	Wald	Sig.	Exp(B)	95% C.I. Exp(B)
Oxidised LDL/albumin	0.160	0.061	6.99	0.008	1.174	1.042 – 1.32
Lymphocytes	-0.282	0.065	19.05	0.000	0.755	0.665 – 0.856
UIC	-0.013	0.003	16.96	0.000	0.987	0.981 – 0.993
K+/Mg <sup>2+</sup> ratio	0.160	0.027	35.83	0.000	1.173	1.113 – 1.236
TSH	0.336	0.132	6.51	0.011	1.400	1.081 – 1.812
FPG	0.441	0.003	5.12	0.024	0.993	0.986 – 0.999
Constant	5.61	2.46	5.22	0.022	272.892	

OxLDL/Alb Ratio: Serum Oxidised LDL cholesterol/Albumin ratio; UIC: urine iodine concentration; FPG: Fasting Plasma Glucose; K+/Mg<sup>2+</sup>: Serum Potassium/Magnesium ratio; TSH: Thyroid stimulating hormone.

### 3.4. The AUC, Optimal Thresholds, Sensitivity and Specificity of the Independent Predictors of Preeclampsia

The AUC, optimal thresholds, sensitivity and specificity at the optimal threshold of those significant biomarkers, are shown in Table 3. The AUC ranged from 0.75 (95% CI 0.69-0.80) for the OxLDL/Alb ratio to 0.97 (0.95-0.99) for K+/Mg<sup>2+</sup>. Sensitivities at optimal threshold ranged from 60% for nitric oxide to 98% for UIC, and specificity from 63.2% for % lymphocyte to 96% for selenium.

**Table 3.** The cut-offs, sensitivity, specificity and areas under the receiver operating curves of various diagnostic biomarkers for the prediction of preeclampsia.

Analyte	Cut off Limit	Sensitivity	Specificity	AUC	95% CI	P
K+/Mg <sup>2+</sup>	>22	93.0 %	95.0%	0.973	0.953 – 0.993	<0.0001
UIC	<239 µg/L	98.0 %	80.0%	0.920	0.893 – 0.946	<0.0001
FPG	>95mg/dL	81.2%	91.3%	0.860	0.822 – 0.897	<0.0001
TSH	>3.9 mIU/L	78.0%	73.0%	0.812	0.771 – 0.854	<0.0001
Lymphocyte %	<23.5	72.7 %	63.2 %	0.773	0.729 – 0.818	<0.0001
OxLDL/Alb Ratio	>7.0	80.0 %	65.0%	0.746	0.695 – 0.797	<0.0001
Selenium	<20 µg/L	79.3%	96.0%	0.885	0.843 – 0.926	<0.0001
Nitric oxide	<10 µg/L	60%	94%	0.784	0.730 – 0.837	<0.0001

OxLDL/Alb Ratio: Serum Oxidised LDL cholesterol/Albumin ratio; UIC: urine iodine concentration; FPG: Fasting Plasma Glucose; K+/Mg<sup>2+</sup>: Serum Potassium/Magnesium ratio; TSH: Thyroid stimulating hormone.

## 4. Discussion

In the current study, the analytes identified as independent predictors of preeclampsia were the oxidized LDL/albumin ratio, lymphocyte levels, urine iodine concentration, serum potassium/magnesium ratio, TSH, and FPG. This suggests the need for closer attention to the role of a high energy-low protein diet, iodine deficiency, subclinical hypothyroidism, magnesium deficiency, and gestational diabetes in the increased risk of preeclampsia in the study population.

Preeclampsia is a multisystem disorder for which clinical symptoms and signs alone cannot adequately predict adverse maternal and foetal outcomes [19]. Previous research in high-resource settings has revealed the potential utility of placental-derived factors for the prediction and early diagnosis of preeclampsia especially the sFlt-1/PlGF ratio [20,21]. Of the variables identified as independent predictors of preeclampsia in the current study, the serum potassium/magnesium ratio had the highest area under the curve. Therefore, the serum potassium/magnesium ratio, which is more affordable compared to the sFlt-1/PlGF ratio, is potentially a candidate screening test for women at high risk of preeclampsia in low resource settings if our results can be confirmed by future studies as recommended by the World Health Organization [22].

In the current study, the median, 25th, and 75th percentile levels of serum magnesium were not only significantly reduced among preeclamptic women compared to normotensive controls, but were

also much lower than the lower limit of normal serum magnesium of 0.74 – 0.95 mmol/L [23,24]. The median levels of serum potassium were comparable (Table 1) between cases and controls, implying that it is the relationship between the individual pregnant woman's potassium and magnesium levels that may determine the risk of preeclampsia. The main known cause of hypomagnesaemia is low dietary intake [25,26]. Globally, the prevalence of hypomagnesaemia is between 2.5 – 15% despite the availability of foods rich in magnesium including whole grains, leafy vegetables and nuts [26]. It is estimated that about 85% of magnesium is lost during food processing putting populations dependent on processed foods at high risk of hypomagnesaemia especially in the era of nutrition transition and urbanization that is sweeping across the developing world [27].

Several other researchers found lower levels of serum magnesium with no significant difference in serum potassium among women with preeclampsia compared to controls [28–33]. Taken together, our findings and those from previous research suggest that the potassium/magnesium ratio may indeed be a good biomarker for the prediction of incident preeclampsia at any gestation age. The high diagnostic potential of the serum potassium/magnesium ratio for preeclampsia, with a specificity and sensitivity in the current study similar to that of sFlt-1/PlGF ratio [5,20] makes it a potential candidate biomarker warranting further exploration for use in resource-limited resource settings and populations at risk. Moreover, both magnesium and potassium are excreted in urine which provides an opportunity for assessing whether the urinary magnesium/potassium ratio may show similar diagnostic performance which may pave the way for even a more affordable urine dipstick potassium/magnesium screening test for preeclampsia that can be used in primary health care clinics.

Magnesium is required for the maintenance of physiological levels of cellular potassium levels [34]. Magnesium is a cofactor of the Na<sup>+</sup>/K<sup>+</sup> ATPase whose malfunction secondary to hypomagnesaemia results in the depletion of intracellular K<sup>+</sup> and accumulation of intracellular Na<sup>+</sup>. This stimulates the Na<sup>+</sup>-Ca<sup>2+</sup> pump exchange activity resulting in high intracellular Ca<sup>2+</sup> with resultant vasoconstriction leading to hypertension [35–37]. Secondly, *in vivo* and *in vitro* studies have confirmed that inadequate magnesium intake/hypomagnesaemia leads to endothelial dysfunction, oxidative stress, insulin resistance and hyperlipidaemia which are known mechanisms in the pathology of preeclampsia and precursors of atherosclerosis [27,38]. Magnesium deficiency increases the transport of low-density lipoproteins across the endothelium whose accumulation in the sub-endothelial space is associated with incident atherosclerosis [38,39]. Hence, hypomagnesaemia coupled with a high-energy diet or obesity may multiply the risk of preeclampsia and cardiovascular disease. Indeed, in one study it was found that carotid intima-media thickness, an early marker of atherosclerosis and cardiovascular disease, was significantly higher among preeclamptic women when compared to normotensive controls [14].

In the current study, the mean urine iodine excretion (UIC) was the biomarker with the second-best diagnostic potential for preeclampsia after the serum K<sup>+</sup>/Mg<sup>2+</sup> ratio. At a cut-off of 239 µg/L, UIC had a sensitivity of 98% and specificity of 80% for the diagnosis of preeclampsia. Previous studies have also shown an association between UIC and preeclampsia [40–42]. Although the standard practice has been the use of median UIC of school-age children (SAC) for the identification of populations at risk of inadequate iodine intake, SAC UIC is not usually representative of pregnant women and other population groups at high risk of iodine deficiency [43,44]. Some have found that there is a daily variation of UIC concentration making it a less accurate measure of iodine nutrition for individualized assessment [45–47]. Rasmussen et al. found that the fasting UIC tends to underestimate the 24-hour UIC compared to samples taken later in the day [48]. However, all UIC values taken at various times of the day were highly correlated with the 24-hour UIC with a correlation coefficient (r) ranging between 0.61-0.74.

About 70 µg of iodine is required for daily thyroid hormone synthesis in an iodine-replete individual with sufficient intra-thyroid iodine storage of 15-20 mg [49]. In physiological pregnancy, the net daily iodine requirements increase to about 120 µg. In chronically iodine-deficient individuals with intra-thyroid iodine storage of about 2-5 mg compensatory mechanisms will increase thyroid iodide trapping by about 50% [49]. In women with moderate to severe iodine deficiency in pregnancy,

most of the iodine consumed will be taken up by the thyroid gland, the placenta and the foetus leading to low serum iodide levels. Hence these women are likely to present with persistently low UIC despite increased renal iodine clearance [49], making UIC a feasible test in pregnant women with moderate to severe iodine deficiency.

Iodine deficiency predisposes to preeclampsia through defective placental angiogenesis in the first trimester which leads to ischaemia, atherogenesis and oxidative stress, diminished PIGF production, increased trophoblastic apoptosis and elevated sFlt-1 secretion leading to maternal systemic endothelial dysfunction [50,51]. In addition, the low serum levels of iodine, one of the most important exogenous anti-oxidants leads to oxidative imbalance and further endothelial activation, dysfunction, and more severe manifestation of preeclampsia [52,53].

In the current study, FPG had the third-best AUC for discriminating pre-eclampsia. Interestingly, the optimal cut-off (95mg/dL) is close to the fasting blood sugar level of 5.3 mmol /L recommended for diagnosis of gestational diabetes by the American Diabetic Association [54]. Therefore, routine screening for diabetes using FPG among pregnant women can also identify women at risk of preeclampsia. This is not surprising as most markers associated with insulin resistance in the current study such as dyslipidaemia and high BMI were significantly higher among cases than controls.

Consistent with other studies [55–57], our data seem to suggest that SCH is associated with preeclampsia as exemplified by T3 and T4 levels within the normal range for both cases and controls, but an elevated mean TSH level for cases of  $5.90 \pm 2.56$  mIU/L well above the recommended pregnancy upper limit of 2.5 - 3 mIU/L. The underlying cause of SCH in the study population seems to be iodine deficiency whose sensitivity and specificity were better than that of TSH. This together with the high cost of TSH would preclude its routine use as a screening test for preeclampsia in low-resource settings.

The fairly good capacity of a lower percentage of lymphocytes as a predictor of preeclampsia observed in the current study could be attributed to the relative increase in neutrophils. Canzoneri et al. found a significantly higher total leukocyte count among women with severe preeclampsia due to the marked increase in neutrophil numbers:  $8.05 \pm 4.01$  (severe preeclampsia) versus  $6.69 \pm 2.23$  (mild preeclampsia) and  $5.90 \pm 1.79$  (controls) respectively,  $p < 0.0001$  [58]. Preeclampsia is associated with the activation of neutrophils and other leukocytes with enhanced superoxide production, and the release of endothelial mediators such as tumour necrotic factor alpha and interleukin-8 that lead to endothelial dysfunction [59,60].

Consistent with other studies the risk of preeclampsia was much higher among women with elevation of both oxidised LDL and triglycerides [61,62]. The oxidised LDL/albumin ratio had a fairly high sensitivity but low specificity probably because low exogenous antioxidant deficiency may play a significant role in the early stages of preeclampsia while renal and hepatic injury associated with a significant reduction in albumin levels occur in late and severe preeclampsia.

As for serum TSH, the low sensitivity and specificity of the lymphocyte percentage and the oxidised LDL/albumin ratio preclude their potential use as potential screening tests for preeclampsia.

### *Study Limitations*

The current study is limited by the case-control study design which precluded the ascertainment of temporal relationship between the observed values of the biomarkers and preeclampsia. The performance of screening tests would better be evaluated with prospective cohort studies, especially for the detection of early-onset preeclampsia that is associated with more perinatal complications [63]. Secondly, the performance of some screening tests may vary according to regional, socio-economic, and ethnic differences which may affect the universal application of the cut-off values [64].

## **5. Conclusion**

The serum potassium/magnesium ratio, which can be obtained from routine laboratory tests, showed a high potential as a biomarker for screening and detection of women at risk of preeclampsia.

The urinary iodine concentration, serum TSH, the oxidized LDL/albumin ratio and FPG, and lymphocytosis may be useful in the prediction of women at increased risk of preeclampsia respectively among populations with iodine deficiency, micronutrient malnutrition, and recurrent infections.

**Supplementary Materials:** The data is available from the authors upon request. This article is a revised and expanded version of a poster presentation at the Clinical Research & Biomarkers conference, July 19-20, 2018, Prague, Czech Republic titled: Serum potassium/magnesium ratio, urinary iodine concentration, thyroid stimulating hormone, fasting plasma glucose and the oxidized LDL/albumin ratio: potential biomarkers of preeclampsia.

**Author Contributions:** BCB conceived and designed the study, participated in data analysis, and wrote the first draft. LMB prepared the data set, participated in the statistical analysis, and edited the first draft. KAP critically reviewed the first manuscript and ensured that the appropriate statistical tests were applied. All authors read and approved the final manuscript.

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**Institutional Review Board Statement:** The study was approved by the Lomo Medical Centre Institutional Review Board (Reference no. LMDE031LMB02). The study was carried out according to the ethical guidelines of the Helsinki Declaration.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The raw data supporting the conclusions of this article will be made available by the authors on request.

**Conflicts of Interest:** The authors declare no conflicts of interest

## Abbreviations

The following abbreviations are used in this manuscript:

Alb	Albumin
BMI	Body Mass index
BMI	Body Mass index
Ca <sup>2+</sup>	Calcium ions
CRP	C-reactive protein
GGT	Gamma Glutamate transferase
HDL	High density lipoprotein
HDL-c	High density lipoprotein cholesterol
LDL	Low density Lipoprotein
LDL-c	Low density lipoprotein cholesterol
L/WBC%	Lymphocyte percentage
Mg <sup>2+</sup>	Magnesium ions
NO	Nitric oxide
OxLDL	Oxidized low density lipoprotein
K <sup>+</sup>	Potassium ions
TSH	Thyroid stimulating Hormone
T3	Triiodothyronine
UIC	Urinary iodine concentration

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