Predictive value of the albumin-to-globulin ratio (AGR) in severe preeclampsia

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Abstract

***Objective*: To demonstrate whether the albumin-to-globulin ratio (AGR) index is a useful marker during pregnancy in order to identify severe preeclampsia and to determine its predictive power.**

***Methods*: A cross-sectional, analytical, and observational study was conducted in a population of Mexican pregnant women with more than 20 weeks of gestation who were included in an outpatient survey, as well as those patients who were admitted to the Women's Hospital of Culiacan, Mexico, from January 2021 to January 2023. Patients with malnutrition or with body mass index (BMI)<19 kg/m^2, patients with chronic renal failure, drug addiction, intestinal malabsorption syndromes, autoimmune diseases, collagen diseases, or myeloproliferative disorders were excluded. Urine samples were collected over 24 hours to measure proteinuria, and blood samples were collected to measure total blood proteins, albumin, globulin, magnesium, calcium, lactate dehydrogenase, uric acid, C-reactive protein, complete blood count, urea, urea nitrogen, and creatinine. The analysis was performed using Stata SE 13 (College Station, Texas 77845, USA).**

***Results*: There were 80 (36.65%) cases of hypoalbuminemia, of which 7 (21.88%) occurred in healthy women, 26 (60.47%) in severe preeclampsia, and the overall frequency of AGR<1.2 was 61 (27.98%), with the highest number of cases in severe preeclampsia. There were 142 (63.68%) patients with other maternal complications and 8 (3.67%) fetal complications. The frequency of AGR<1.2 was 6 (18.75%) in healthy women and 19 (45.24%) in severe preeclampsia (p=0.0178). The AGR<1.2 was significantly associated with severe preeclampsia (OR=3.57, p=0.0201).**

***Conclusion*: The presence of an AGR lower than 1.2 is associated with severe preeclampsia with greater specificity than albumin alone.**

Keywords: Severe preeclampsia, albumin-to-globulin ratio, AGR.

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Introduction

Preeclampsia is a multifactorial disease, and its pathophysiology remains incompletely understood. The main clinical features are proteinuria greater than 300 mg in a 24-hour urine sample and hypertension. Preeclampsia is characterized by an imbalance of angiogenic and anti-angiogenic factors leading to placental failure and secondary systemic endothelial dysfunction involving the renin-angiotensin-aldosterone system (RAAS) and complement system, which has a significant impact on maternal and perinatal morbidity and mortality. (1–3) In a normal pregnancy, blood pressure decreases, leading to increased circulating RAAS to compensate. However, under normal circumstances, blood pressure does not rise significantly due to the refractory effect of angiotensin II. This effect does not occur in preeclampsia; therefore, blood pressure increases considerably due to angiotensin II. (4)

In 1946, Leon and Braier observed that, due to the small molecular weight of albumin, there was increased leakage of this molecule to the interstitial tissue during pregnancy. In addition, there is a state of nephrosis in which albumin is excreted in the urine, thereby decreasing plasma albumin levels. In contrast, globulin tends to increase or appear to increase because of its higher molecular weight, without urinary excretion. (5)

During pregnancy, albumin acts as an essential extracellular scavenger of toxins, an antioxidant, and a source of amino acids for cell and matrix synthesis. There is a proinflammatory state that has been described during pregnancy in patients with preeclampsia that also leads to the development of hypoalbuminemia. (5–7)

To the best of our knowledge, there is currently no marker or laboratory test in the primary care setting in Mexico that can help clinicians anticipate the onset of severe preeclampsia. However, some tertiary hospitals use prognostic markers for preeclampsia, such as the sFlt-1/PlGF index, which are primarily used to determine their usefulness in early- or late-onset preeclampsia. There is also a Doppler ultrasound of the uterine arteries, which has a sensitivity of 20%-60% and a positive predictive value of 6%–40%, resulting in a weak diagnostic yield. Primary care centers typically lack access to a Doppler ultrasound. (6,8–10)

Some studies have shown that the albumin-to-globulin ratio (AGR) is among the indices of systemic immune inflammation and is an adverse prognostic factor in chronic kidney disease, severe forms of coronavirus disease 2019 (COVID-19), heart disease, and certain malignancies, including cervical cancer. (11–14)

Studies trying to elucidate the relationship of hypoalbuminemia with severe pre-eclamptic forms and their maternal-fetal outcomes have been carried out, but they have inconsistent results and methodological flaws. (5,6,9,15)

In a study conducted in 2011 in Canada by Benoit J et al. on pregnant women at less than 37 weeks of gestation with severe preeclampsia, it was demonstrated that an albumin level of less than 2 g/l compared to non-severe pre-eclamptic women may have been a prognostic factor. However, it was not possible to consider it an independent prognostic marker of severe preeclampsia because of confounding among the included patients, owing to comorbidities and other adverse conditions; therefore, a possible association could not be demonstrated. (16)

Relatively little is known about the AGR as a prognostic marker during pregnancy to predict severe preeclampsia. Therefore, it is imperative to demonstrate the utility of this index in pregnant women in the second trimester, so that it can be used early as an adverse prognostic marker and to inform timely preventive decisions, even during outpatient follow-up.

The objective of the present study was to demonstrate whether the AGR was an adverse marker during pregnancy for severe preeclampsia and to determine its predictive power for severe preeclampsia.

Material and methods

A cross-sectional, analytical, and observational study was conducted in a population of pregnant women at more than 20 weeks' gestation, including those consecutively enrolled in the survey from preconsultation and those hospitalized in the maternity ward at the Women's Hospital, from January 2021 to January 2023. The cases were diagnosed by physicians specializing in gynecology and obstetrics, excluding patients who were malnourished or with a body mass index (BMI) <19 kg/m^2, patients with chronic renal failure, drug addiction, intestinal malabsorption syndromes, autoimmune diseases, collagen diseases, or myeloproliferative disorders.

Case definition

Severe preeclampsia: pregnant with blood pressure ≥160/110 mmHg plus proteinuria greater than 300 mg in a 24-hour urine collection at 20 weeks of gestation; or in the absence of proteinuria, blood pressure ≥140/90 mmHg associated with any of the following criteria:

a. Oliguria (urine <0.5 cc/kg/hr)
b. Serum creatinine >1.1 mg/dl
c. Neurologic or visual disturbances (hyperreflexia with clonus, severe headache, scotomas,

blurred vision, amaurosis)
a. Pulmonary edema
b. Epigastric or right hypochondrial pain
c. Changes in liver function tests: glutamic-oxalacetic transaminase (GOT) or glutamic-pyruvic transaminase (GPT) >70 U/l, lactate dehydrogenase (LDH) >600 U/l
d. Hematologic alterations: thrombocytopenia (<100,000 platelets/l)
e. Intrauterine growth retardation (IUGR) with growth less than P10 for gestational age
f. Oligohydramnios: amniotic fluid index (AFI)<5 cm

Definition of controls

Healthy pregnant women at >20 weeks' gestation were followed concurrently with the cases.

All patients signed the informed consent form, which was approved by the Women's Hospital Ethics Committee (registry no. 202410-66).

Alternative hypothesis

AGR<1.2 is an adverse prognostic index during pregnancy for the development of severe preeclampsia.

Null hypothesis

AGR<1.2 is not an adverse prognostic index during pregnancy for the development of severe preeclampsia.

Methods

A total of 149 consecutive pregnant women, 32 healthy, 42 with severe preeclampsia, 33 with gestational hypertension (GHT), and 42 with non-severe preeclampsia, were evaluated. Only healthy women and those with severe preeclampsia were included in this study, and the presence of pregnancy-related complications was also examined. Urine samples were collected for 24-hour proteinuria, and blood samples were taken for total blood proteins, albumin, globulin, magnesium, calcium, lactate dehydrogenase, uric acid, C-reactive protein, complete blood count, urea, urea nitrogen, and creatinine. The data were processed using the Wiener Lab CM320i compact benchtop analyzer for clinical chemistry and immunoturbidimetry.

Statistical analysis

Measures of central tendency and dispersion were computed for quantitative variables, and frequencies and percentages were calculated for qualitative variables. The optimal cut-off point for the AGR was determined using the Youden index based on the receiver operating characteristic (ROC) curve. Subsequently, its predictive diagnostic performance in patients with severe preeclampsia was assessed, and the strength of the association between severe preeclampsia and AGR <1.2 was evaluated. The odds ratio (OR) for the study population was estimated using univariate logistic regression, with a significant association defined as $p<0.05$. Healthy pregnant women were the reference population and were contrasted with those with severe preeclampsia. The analysis was performed using Stata SE 13 (College Station, Texas 77845, USA).

Results

Overall, the study population consisted of 149 pregnant women with a mean age of 25 years, a gestational age of 37.8 weeks, and a mean number of gestations of 2, with a minimum of 1 and a maximum of 8 gestations (**Table 1**).

Measures of central tendency and dispersion of albumin and globulin levels indicated that the highest albumin levels were observed in healthy pregnant women. In contrast, the highest globulin levels were observed in severe preeclampsia (**Table 2**).

Measures of central tendency and dispersion of AGR in healthy women and women with severe preeclampsia are shown in **Table 3**.

There were 80 (36.65%) cases of hypoalbuminemia, of which 7 (21.88%) occurred in healthy women, 26 (60.47%) in severe preeclampsia, and the overall frequency of AGR<1.2 was 61 (27.98%), with the highest number of cases in severe preeclampsia. There were 142 (63.68%) other maternal complications and 8 (3.67%) fetal complications.

The frequency of AGR<1.2 was 6 (18.75%) in healthy women and 19 (45.24%) in severe preeclampsia ($p<0.0178$). AGR<1.2 was significantly associated with severe preeclampsia (OR=3.57, p=0.0201) (**Table 4**).

Discussion

This study aimed to evaluate whether an AGR of less than 1.2 during pregnancy is an adverse prognostic factor for severe preeclampsia and to estimate its predictive value for severe preeclampsia and maternal-fetal complications.

Hypoalbuminemia has long been shown to be an adverse prognostic factor in severe infectious processes, such as COVID-19, hospital-acquired pneumonia, severe burns, or neoplastic processes. Similarly, a low AGR (<1) is an adverse prognostic factor in COVID-19, as this index is more frequently observed in severe forms and in non-survivors, which has also been observed (index <1.345) in surgically treated cervical cancer patients (10,12,15).

In the present paper, we observed that severe pre-

eclampsia was 3.57 times more likely when the AGR level was <1.2. Similarly, the presence of hypoalbuminemia was observed 3.4 times more often in severe preeclampsia.

With these obtained results, we can confirm that AGR<1.2 and hypoalbuminemia are risk factors for the most severe forms of pregnancy-induced hypertension, in which morbidity and mortality are higher. (6)

Although studies have been performed in preeclamptic patients on the prognostic relationship of hypoalbuminemia with severe forms as well as their maternal-fetal outcomes, (5,15) relatively little or almost nothing is known about an AGR of less than 1.2 as a risk marker during pregnancy. Therefore, it would be worthwhile to demonstrate the efficacy of this marker by conducting longitudinal studies with larger populations in the second trimester of pregnancy to determine its usefulness earlier in medical decision-making at the first level of care.

It was also demonstrated that AGR has a higher specificity than hypoalbuminemia for predicting severe preeclampsia during pregnancy (**Table 5**, **Figure 1**).

The main strength was to demonstrate that AGR<1.2 was strongly associated with severe and early preeclampsia, which would be a valuable tool for taking early and timely treatment measures to prevent severe complications in pregnant patients. On the other hand, we confirmed that hypoalbuminemia during pregnancy was an adverse factor for the development of severe forms of preeclampsia as well as maternal and fetal complications.

A limitation of this study was that, for AGR<1.2, we could not identify comparable studies for comparison with our results, and the sample size was small.

Conclusion

An AGR<1.2 is a factor associated with severe preeclampsia and is more specific than albumin alone. However, prospective longitudinal studies with larger populations, beginning in the second trimester of pregnancy, are needed to demonstrate its utility in early pregnancy at the first level of care.

Table 1. Gestational age and profile of patients

	Healthy	Severe preeclampsia	Statistical significance
Age (years)	25.7	26.04	0.83
Gestational weeks (weeks)	36.6	36.6	1.00
BMI (kg/m^2)	29.5	30.6	0.43
Leukocytes (/ul)	11,648	10,529	0.12
Platelets (/ul)	190,000	210,000	0.37
CRP (mg/l)	59.4	34.36	0.21
DHL (mg/l)	209	285	0.057
Creatinine (mg/l)	0.56	0.60	0.21
Urea (mg/l)	17	19.5	0.13
UN (mg/l)	7.85	12	0.22
24-hour urine protein (mg)	-	1,297±2,012	-
Uric acid (mg/l)	4.66	5.61	0.0061
Calcium (mg/l)	9.29	8.93	0.0175
Mg (mg/l)	1.86	2.04	0.0947

Table 2. Measures of central tendency and dispersion of albumin, globulin, and AGR levels by groups of pregnant women

	Albumin			Globulin			AGR
	Mean	Median	SD	Mean	Median	SD	
Healthy	3.64	3.71	0.46	2.68	2.7	0.39	1.35
Severe preeclampsia	3.39	3.41	0.34	2.75	2.75	0.44	1.23

Legend: AGR=albumin-to-globulin ratio; SD=standard deviation.

Table 3. Measures of central tendency and dispersion of AGR values in healthy and severe preeclampsia

Groups	Average	Median	SD	Minimum	Maximum
Healthy	1.44	1.42	0.29	0.93	2.6
Severe preeclampsia	1.28	1.26	0.23	0.75	1.86

Legend: AGR=albumin-to-globulin ratio; SD=standard deviation. p-value=0.008.

Table 4. AGR<1.2 and risk of severe preeclampsia

Odds ratio	3.5797
95% confidence interval	1.2208 to 10.4964
z statistic	2.324
Significance level	p=0.0201

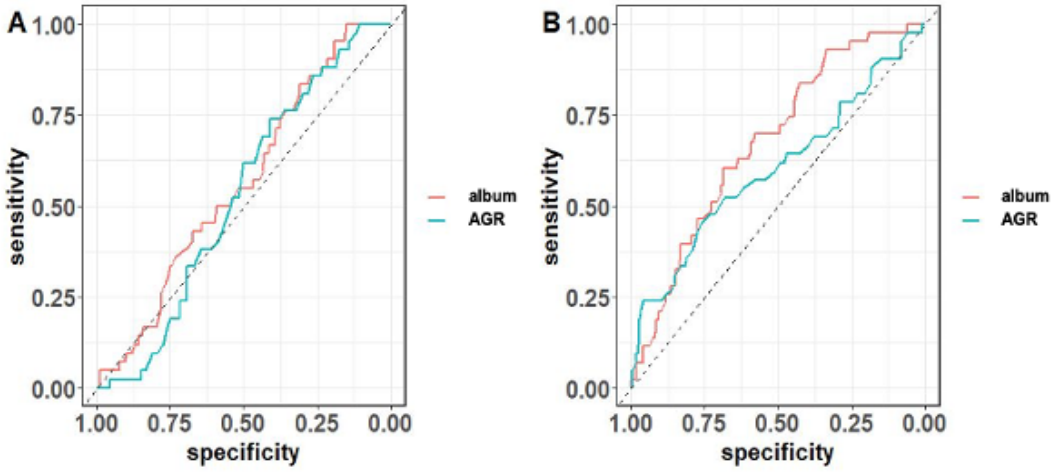
Legend: AGR=albumin-to-globulin ratio.

Table 5. Diagnostic yield of AGR<1.2 in patients with severe preeclampsia

	Prev	Sensi-tivity	Speci-ficity	PPV	NPV	LR+	LR-	Precision	A	FPR	FNR
AGR<1.2	45.23	45.24	81.25	66.58	64.24	2.41	0.67	64.96	0.60	18.75	46.93

Legend: AGR=albumin-to-globulin ratio; Prev=disease prevalence; PPV=positive predictive value; NPV=negative predictive value; LR+=positive likelihood ratio; LR-=negative likelihood ratio; A=accuracy; FPR=false positive rate; FNR=false negative rate.

Figure 1. Diagnostic performance of the predictive model albumin-globulin ratio using ROC curve for severe preeclampsia



Model	AUC	Optimal_Cutoff	Sensitivity	Specificity
pens_album	0.5626850	3.110	1.0000000	0.1525424
pens_AGR	0.5286120	1.285	0.7380952	0.4090909
pese_album	0.6756078	3.495	0.6046512	0.6875000
pese_AGR	0.6020022	1.225	0.4523810	0.7613636

Legend: ROC=receiver operating characteristic; album=albumin; AGR=albumin-to-globulin ratio; AUC=area under the curve; pens_album=albumin in non-severe preeclampsia; pens_AGR=albumin-to-globulin ratio in non-severe preeclampsia; pese_album=albumin in severe preeclampsia; pese_AGR=albumin-to-globulin ratio in severe preeclampsia.
Model A is for non-severe preeclampsia, and model B is for severe preeclampsia. Optimal values was obtained with the Youden index.

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