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Prediction of preeclampsia with the determination of serum homocysteine. A single-center observational study.

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Abstract

Introduction: The present study aimed to evaluate homocysteine levels as a predictor of preeclampsia in pregnant patients aged 12 to 20 weeks.

Methods: This was observational, longitudinal, and prospective research. The study population included patients who attended their first prenatal care visit between 12 am and 8 pm, and the random sample included 360 patients whose serum homocysteine concentration was determined. Forty-eight pregnant women who did not meet the exclusion and inclusion criteria were excluded.

Results: Homogeneity was found among the patients; 270 patients (86.5%) had a normal pregnancy, 27 women (8.65%) had gestational hypertension, 9 (2.88%) had mild preeclampsia, and six patients (1.9%) had severe preeclampsia. -eclampsia; no patients had HELLP syndrome. An increase in homocysteine levels was observed in 9 women who were not diagnosed with hypertensive disorders during pregnancy.

Conclusions: In the present research, homocysteine levels were not found to be a predictor of hypertensive disease during pregnancy.

Keywords:

DeCS: Homocysteine; Preeclampsia; Hypertension, Pregnancy-Induced; Eclampsia.

Abbreviations
Not declared.

Supplementary information
No supplementary materials are declared.

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Author contributions
Ramón Miguel Vargas-Vera: Conceptualization, data curation, formal analysis, acquisition of funds, research, writing - original draft, writing – review, and editing.
Martha Verónica Placencia-Ibadango: Conceptualization, data curation, research, writing - original draft, Validation, Visualization.
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Not declared.

Introduction

Hypertensive disorders during pregnancy, such as preeclampsia (PE) and eclampsia, are of placental origin but of unknown cause. Various theories have been proposed, but none explain the pathophysiological events that determine this process. Genetic, family, environmental, immunological, and individual factors that interact in various ways have been attributed to its appearance. The common denominator is the alteration of uteroplacental circulation resulting from incomplete replacement of the muscular layer in the spiral arterioles by trophoblast cells at 12 to 14 weeks and 16 to 18 weeks of pregnancy [1].

Alterations in the metabolism of methionine-homocysteine (Hci), which may be related to systematic vascular damage, have been found and may lead to the classic clinical manifestations of hypertensive disorders during pregnancy. It is also assumed that high Hci may contribute to the development of placental microvascular diseases and PE, negatively affecting the endothelium. Women diagnosed with PE are at increased risk of future cardiovascular or cerebrovascular disease compared to unaffected women. Hyperhomocysteinemia is a risk factor for cardiovascular disease, peripheral vasculature, cerebrovascular disease, cognitive dementia disorders, neurodegeneration, and fractures associated with osteoporosis. It could be genetically related to folate deficiency [2].

Hyperhomocysteinemia in preeclampsia is attributed to a deficiency in folate concentration due to a deficiency of folic acid or an alteration of the metabolism of the enzyme methylenetehydrofolatereductase (MTHFR). Other possible mechanisms are attributed to tissue damage, oxidative stress, metabolic syndrome, or inflammatory processes. Some researchers believe this increase is due to increased xanthine oxidase activity [2].

HCl levels in the serum of pregnant women were measured with a reference value of up to 10 mmol/dl. The association between homocysteine and vascular disorders has been debated in recent decades. In one study, 11 of 58 severe PEs (19%) at 28 weeks were determined to be associated with hyperhomocysteinemia. An increase in homocysteine concentration has been observed in pregnant women with preeclampsia compared to healthy pregnant women in the third trimester; thus, the prevalence of hyperhomocysteinemia is more significant in patients with hypertensive disorders than in controls [3].

The development of PE due to the increased sensitivity of the uteroplacental vasculature during pregnancy is a product of hyperhomocysteinemia, which can persist for the remainder of life, predisposing patients to coronary artery disease or late vascular disease after pregnancy and continuing for the remainder of life. Several predictive risk factors for the development of PE before clinical presentation have been described [4].

According to this background, there are risk factors related to this pregnancy pathology that have a high rate of perinatal maternal mortality (MMP), but the etiological situation and how to predict it are still unclear. Several algorithms have been proposed to predict PE; however, these algorithms are encouraging and should be validated. Simple preventive measures, such as low-dose aspirin, calcium, and diet and lifestyle interventions, show some potential benefits [5].

According to the World Bank (2014), the average expenditure on health care is estimated to be $579 per year per person in low-income countries, and preconception care protocols are not carried out; if they exist, they are deficient; thus, we observe that preconception and postconception folic acid supplementation do not follow international protocols. In pregnancy pathologies, screening is not performed in asymptomatic stages such as gestational diabetes and DHE [6].

In our country, particularly at the University Hospital of Guayaquil (HUG), there are no preconception care programs; likewise, prenatal care is deficient, and routine control programs are inadequate for patients concerning the dosage of folic acid and the determination of Hci in the serum. Patients usually attend their first prenatal check-up starting in the second trimester.

One of the signs that appears to be associated with preeclampsia is hyperhomocysteinemia, but this topic of debate is that it is considered a prediction tool. This research aimed to evaluate the importance of homocysteine levels as a predictor of preeclampsia in pregnant patients aged 12 to 20 weeks and whether homocysteine levels predict pregnancy.

Materials and methods

Study design

The present study was observational and descriptive. The source is prospective.

Scenery

The study was conducted at the outpatient gynecology and obstetrics service of the University Hospital of Guayaquil in Guayaquil, Ecuador. The study period was from October 1, 2018, to October 30, 2019.

Participants

Pregnant women between 12 and 20 weeks and under 40 years of gestation were included. Patients who presented other associated diseases during pregnancy, such as type 2 diabetes mellitus and arterial hypertension, were excluded. Patients who did not attend the follow-up check according to their clinical history and those who terminated their pregnancy at another institution were excluded.

Variables

The independent variable was hyperhomocysteinemia, and the dependent variable was preeclampsia–eclampsia. Other variables, such as body mass index (BMI), maternal morbidity, and birth weight, were evaluated.

Data sources/measurements

The sources were mixed, direct and indirect; electronic consent was obtained using data from medical records and patient surveys. In the hospital's clinical laboratory, a peripheral blood sample was taken from the patients at 12 to 20 weeks of gestation to determine the serum homocysteine concentration; a homocysteine concentration of 12 µmol/dL was used as the cutoff point.

The patient was considered preeclampsia if they had blood pressure values of 140/90 mm Hg or more, as verified at least twice in 4-6 hours, or if the blood pressure after 20 weeks was associated with proteinuria: ≥ 300 mg in 24 hours.

Biases

To avoid interviewer, information, and memory biases, the leading researcher always maintained the data with a guide and records approved in the research protocol. Observation and selection bias were avoided by applying participant selection criteria. Two researchers independently analyzed each record in duplicate, and the variables were registered in the database once their agreement was verified.

Study size

The reproductive age population in the Guayas is 1170098 women aged between 15 and 49 years. According to the 2021 National Health and Nutrition Survey (ENSANUT), the incidence of pregnancy in Ecuador was 12.1%. This percentage represents 140,411 possible pregnancies per year as a whole. The EPI Info™ program (version 7.2.5, CDC, Atlanta, USA, September 2022.) With an expected frequency of 20%, confidence limits of 5%, and a confidence level of 97%, the sample size was 301 patients.

Quantitative variables

Descriptive and inferential statistics were used. The results of categorical variables are expressed as the frequency and percentage. The scaled variables are defined as the mean and standard deviation.

Statistical analysis

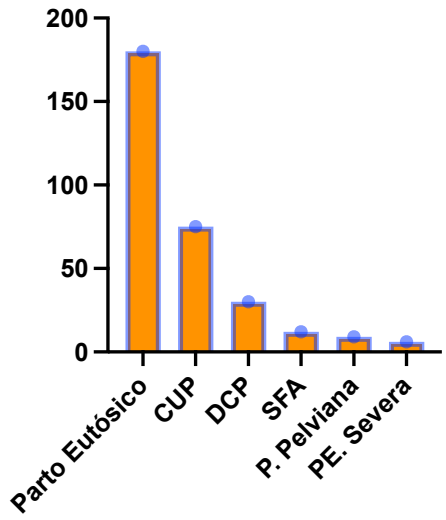
Inferential statistics were used for comparative analysis between the groups. Categorical data were analyzed, and the chi-square test was used to establish associations or differences. The SPSS statistical package was used for the analysis (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Participants

The study included 312 pregnant women. Forty-eight patients were excluded due to a history of current multiple pregnancies, chronic arterial hypertension, cardiovascular disease, chronic kidney disease, treatment with antifolates, diabetes mellitus, or age >40 years.

Figura 1. Culminación del embarazo.



Description of the study group

There were 312 pregnant women, most between 20 and 24 (Table 1). Fifty-eight percent of the patients were from urban areas, 23% were from rural areas, and 19% were from marginal urban areas. Seventy-two patients had more than two previous partners (23.1%). Systolic blood pressure and diastolic blood pressure did not significantly change. The study population had the same characteristics in terms of taking folic acid. Concerning the risk factors studied, we observed that

maternal age, parity, and low intake of foods rich in folates are essential (Table 2).

Of the 312 pregnant women, 270 (86.5%) had a normal pregnancy, 27 (8.7%) had gestational hypertension, 9 (2.9%) had mild preeclampsia, 6 (1.9%) had severe preeclampsia, and 21 (6.7%) had proteinuria and did not develop HELLP syndrome. The classification according to gestational age is presented in Table 3.

Homocysteinemia study

Homocysteine concentrations did not significantly change; of the 312 pregnant women, only nine patients (2.9%) had elevated serum homocysteine concentrations ranging from 13 to 15 µmol/L, and 303 patients (84.5%) had homocysteine concentrations ranging from 5 to 12 µmol./L.

The most crucial point, which was identified as hypertensive disorders during pregnancy, was not statistically significant (P =0.454), with a 13.5% incidence of hypertensive disease (Table 4).

Of the 312 women who participated in the research, 15 (4.8%) presented with PE. The Hci levels of these patients and those who had a normal pregnancy were not significantly different (P =0.088) from those of patients with PE (P =0.03766518) and those patients with gestational hypertension (Table 4).

Diagnostic tests

These results give us a sensitivity of 28.12%, a specificity of 47.12%, and a negative predictive value of 49.52% for PE. The positive predictive value was 2.29%.

The completion of the pregnancy occurred without complications in all patients; they continued with periodic prenatal check-ups and the intake of iron, calcium, and folic acid. Regarding the termination of pregnancy, 57.7% of the pregnant women died during standard delivery, and 42.3% died during cesarean section for the following reasons: 22.7% had cephalopelvic disproportion due to pelvic dystocia, 56.8% had a previous cesarean section, 9.1% had acute fetal distress, 6.8% had this condition due to pelvic presentation, and 4.5% had this condition due to severe preeclampsia (Figure 1). The average weight of the newborns was 3227 grams + 407.

Table 1. Characteristics of the population.

Variable		Patients N=312(%)
Age	< 19 years	63(20.2%)
	> 35 years	33(10.6%)
	20 – 34 years	216(69.2%)
Starting Weight		65.64 + 15.01
Systolic BP		110 (66-144)
Diastolic BP		68 (44 - 98)
Weight gain		129(39.1%)
Proteinuria		21(9.1%)
History of PE	Yes	96 (30.7%)
	No	216 (69.3%)
Gestation	Primigesta	111(35.6%)
	Multiparous	201(64.4%)

PE: preeclampsia.

Table 2 . Risk factor is in the population

Variable		n=312(%)
Age gestational	< 15 weeks	141(58.0%)
	16-20 weeks	108 (42.0%
Civil status	Free Union	171(54.8%)
	Catholic	69 (22.1%)
	Married	72 (23.1%)
Job	Student	42 (14.3%)
	Housewife	162 (55.1%)
	Others	90 (30.6%)
Instruction	Primary	75 (23.1%)
	Secondary	177 (56.1%)
	Superior	60 (19.2%)
Home	Rural	72 (23%)
	Urban	183 (58.7%)
	marginal urban	58 (19%)
Pregnancies	Primigesta	108 (46.4%)
	Multiparous	204 (53.6%)
Couples	A	237 (76.9%)
	More fingers	75(23.1%)
acid intake folic	No	36 (11.5%)
	Preconception	57 (18.3%)
	Postconception	219(70.2%)
Food rich : cereal/vegetable	1-2 times	168 (53.8%)
	Over 3	144 (46.2%)
Rich foods in meats	No	12 (3.8%)
	1-2 times	159 (51%)
	Over 3	141(45.2%)
	Normal	297 (90%)

Table 3 . Hypertensive Gestational by age gestational groups.

Pregnancy by week gestational .	< 19 SG n=63	20 – 34 GS n=216	> 35 SG n=33	Total n=312
Normoevolutionary	54 (85.7%)	201 (93.%)	15 (45.6%)	270
Hypertension Gestational	6 (1.92%)	12 (3.85%)	9 (2.88%)	27
Mild PE	3 (0.96%)	0 (0%)	6 (1.92%)	9
Severe PE	0 (0.0%)	3 (0.96%)	3 (0.96%)	6

SG: week gestational . PE: preeclampsia.

Table 4 . Comparison of Homocysteine between patients with PE and pregnancy norm evolutionary .

Variable	Hypertension Gestational (n=27)	PE (n=15)	Norm evolutionary (n=270)
Homocysteine (um/L)	11.05 ± 1.28	12.05 ± 1.29	10.13±1.65

PE: preeclampsia.

Discussion

One of the leading causes of perinatal morbidity and mortality is hypertensive disorders during pregnancy, which can be related to the extreme conditions of reproductive age, which are usually associated with hypertensive disorders in women [7, 8]; however, our research did not observe this risk factor in adolescents aged >19 years or >35 years. For many years, attempts have been made to investigate the factors and clinical data that allow us to predict the disease before the clinical picture appears. However, this phenomenon has not been significantly reported [9 -11]. In 2009, Guven et al. observed hyperhomocysteinemia in pregnant women with preeclampsia in the third trimester compared to healthy pregnant women [12]; therefore, it has been proposed that homocysteine levels could predict preeclampsia [13-19]. Several studies have postulated that hyperhomocysteinemia promotes the endothelial damage characteristic of PE and impacts intrauterine development [20- 22].

Other authors report that hyperhomocysteinemia levels in early pregnancy are associated with the later appearance of mild PE [7]. Kharb et al. said that Hci levels were slightly more remarkable in the maternal blood of hypertensive pregnant women than in that of normotensive pregnant women ($P < 0.001$ and $P > 0.05$, respectively). It has been shown that vitamin B12, serum homocysteine, and folic acid levels may be altered in preeclampsia [24]; increased homocysteine and low folic acid values are associated with PE [6, 25]. However, in the study published by Wadhwani et al. evaluating maternal plasma folate, vitamin B12, and HCl levels in women with normotensive control (NC) and women with PE from early pregnancy to delivery [26], maternal plasma homocysteine levels were more significant in PE patients than in healthy pregnancy controls. These results indicate higher levels of homocysteine in women with PE from early pregnancy to delivery; these results are discordant with the present investigation. Andrey et al. revealed that HCl levels are altered in uncomplicated and complicated pregnancies; in some reviews, HCl levels tend to decrease during subsequent pregnancy periods [27].

The present investigation did not reveal an increase in homocysteine levels, and hyperhomocysteinemia was increased in 9 patients who did not develop PE. However, Sun F et al. revealed that a hyperhomocysteinemia concentration is an independent risk factor for severe first-trimester PE [28]. These results yielded a sensitivity of 28.12% and a specificity of 47.12%, with a positive predictive value of 2.29% and a negative predictive value of 49.52% for PE.

In the maternal blood of hypertensive pregnant women, vitamin B12 levels were lower than those in normotensive pregnant women, suggesting that folate vitamin B12 deficiency and high HCl during pregnancy may be risk factors for PE and a future of cardiovascular risk [29]. Our results do not

agree with these publications because HCl levels did not establish a direct relationship with the development of PE. This could be explained by a diet enriched with folic acid and 5 mg of folic acid supplementation since they were first included in the study. The patients, which caused their presentation to decrease. Therefore, recommending the administration of folic acid during pregnancy reduces the possibility of PE by lowering homocysteine levels, which was not successful in our work; moreover, our findings are comparable to those published by Mujawar et al. [24] in 2011, which revealed that homocysteine concentrations are negatively correlated with PE [29].

In the United States, 20% of the population does not consume foods rich in folic acid, and its incidence is similar to that of the rest of the population, which supports the notion that folic acid levels do not have a predictive role in the development of PE [12].

It is currently accepted that increased levels of homocysteine are a cardiovascular risk factor that can cause damage to the endothelium of veins and arteries, limiting the ability to incorporate deoxyuridine, which includes the placental vasculature, by increasing the dose of folic acid during pregnancy, as a protective factor against developing preeclampsia [20, 36]. Folic acid supplemented with L-arginine in food could prevent PE by improving endothelial function [1].

Evidence of hyperhomocysteinemia as a predictor of PE in pregnant women can be observed. Our study did not provide significant results because the foods of these individuals were fortified with folic acid, suggesting that exogenous administration of folic acid does not significantly impact the development of PE. This allows us to establish guidelines for conducting randomized, placebo-controlled, and double-blind investigations, allowing us to confirm the dose and its relationship with preeclampsia. The recommended daily dose is 1 to 5 mg to reduce the risk of neural tube closure defects [30].

DHE is one of the leading causes of MMP, and severe complications in newborns, including low birth weight, premature birth, placental abruption, and chronic functional limitations, can lead to maternal death. No strategies help prevent or cure these conditions [1, 2, 7, 31, 32].

The purpose of reducing the prevalence of maternal and fetal complications that are a product of hypertensive disorders during pregnancy is our priority. In Ecuador, 43 deaths were estimated to have occurred in 2013 due to this cause, which translates into a maternal mortality rate of 43 per 340,000 newborns [33]. The prevalence of preeclampsia in its two mild and moderate forms is 5 to 8%, which can reach 10%, with a rate of maternal-fetal mortality, prematurity, intrauterine growth retardation, and premature placental abruption [34, 35].

The prevalence of hypertensive disorders during pregnancy in the present investigation was 13.5%, which coincides with what has been reported in the literature. A total of 8.7% of the cases were attributed to gestational hypertension, and 4.8% were attributed to preeclampsia. Concerning sociodemographic, personal pathological, and gynecological-obstetric risk factors, there were no significant differences ($P = 0.0088$), nor were there any published in the medical literature [32].

In this research, several limitations were evident. Initially, a larger sample size was planned to be used; high doses of folic acid did not reduce the PE index, and a deviation of the trend toward the left was observed where higher proportions of hypertensive disease occur during pregnancy. However, these differences were not statistically significant. A study is recommended to search for equivalences to hypertensive treatments during pregnancy.

Along with other risk factors, homocysteine levels could be a predictive marker for hypertensive disorders during pregnancy, allowing us to make a timely diagnosis and thus avoid complications during treatment.

However, experimental studies are needed to identify and prophylactically treat pregnant women at risk of preeclampsia and hyperhomocysteinemia by improving their lifestyle, limiting their salt intake during pregnancy, and allowing them to rest in the left lateral decubitus position to reduce the prevalence of this disease.

Determination of the serum homocysteine concentration is recommended in a larger population and at many centers to increase the sample size and reduce the degree of imprecision and variability in our research.

Conclusions

The measurement of serum homocysteine levels was not specific or sensitive for predicting preeclampsia in the present investigation.

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Statements

Ethics committee approval and consent to participate

The bioethics committee of the Guayaquil University Hospital approved the study.

Publication consent

Patient-specific images, X-rays, and studies were not available for publication.

Conflicts of interest

Ramón Miguel Vargas-Vera is a shareholder of the Center for Genetic and Perinatal Studies (CEPEGEN). No other conflicts of interest are reported.

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