HOMOCYSTEINE IN PREGNANCY AS A PREDICTOR OF PRE-ECLAMPSIA

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ABSTRACT

Background. For more than 3000 years, medical conditions known as hypertensive states of pregnancy have been described. Hippocrates described epileptic seizures, while in the first century Celsus linked epileptic seizures to fetal death. Galen distinguished between epilepsy and peripheral epilepsy. Maternal mortality due to epilepsy reaches 44% and perinatal mortality reaches 27.8%. Homocysteine is related to PE between 20 and 30%, and an increase in PE or hyperhomocysteine may be the result of a genetic defect in the enzyme methylenetetrahydrofolate reductase (MTFHR) that is involved in homocysteine synthesis. The purpose of this study was to identify homocysteine levels in pregnant women between 16 and 20 weeks as an indicator of the likelihood of developing preeclampsia. Material and method. - It was an observational, longitudinal and prospective research. The study population consisted of patients who attended the first prenatal care consultation between 16 and 20. weeks, the sample was randomized that included 312 patients who were determined to have serum homocysteine. Results. 270 patients (86.5% of the total) had a normal pregnancy. 27 patients (8.65%) developed gestational hypertension, 9 (2.88%) had mild PE, and 6 (1.9%) had none developed HELLP syndrome. Homocysteine levels in patients with preeclampsia were in the standard range (11.05). Conclusions. In the current analysis, the frequency of hypertensive disease in pregnancy was found to be 13.5%. There is no correlation found between homocysteine levels and the development of hypertensive disease during pregnancy.

Keywords: Homocysteine. EP. Gestational hypertension. Hypertensive gestosis.

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INTRODUCTION

Hypertensive disorders of pregnancy (HUD) represent the second leading cause of death in pregnant women in developed nations and the leading cause of health problems and mortality in neonates. Preeclampsia (PE) represents a significant factor in maternal, fetal and neonatal morbidity, particularly in low-income countries. media. In 2010, it was identified as the main cause of death of pregnant women in Ecuador according to the INEC of that year. In a recent study, the prevalence of DUS was 7%, which is significantly less than the 10% expected1,2.

Some algorithms for predicting PE have been developed and are encouraging, which need to be validated. Simple preventive measures, such as low-dose aspirin, calcium, and diet and lifestyle interventions, show some potential benefit2.

It has been found that alterations in methionine-homocysteine (Hci) metabolism may be related to systematic vascular damage, which can lead to the classic clinical appearance of DHE. It is also assumed that higher levels of 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 increases the risk of cardiovascular diseases, peripheral vascular diseases, cerebrovascular diseases, cognitive-dementia disorders, neurodegenerative disorders, and fractures associated with osteoporosis. The increase in Hci. it can be of genetic origin or related to folate deficiency3.

Hci is an amino acid, which is measured in serum in pregnant women with a reference value of up to 10 mmol/dl. In our country and particularly in the University Hospital of Guayaquil (HUG) there are no preconception care programs, likewise prenatal care is deficient and routine control programs are not adequate in patients with respect to the dosage of folic acid and the determination of Hci in the serum; Patients usually go to the first prenatal control from the second trimester.

According to the World Bank (2014), it is estimated that the average expenditure on health care is 579 dollars per year per person in low-income countries; and preconception care protocols are not carried out and if they exist they are deficient, thus we observe that preconceptional and postconceptional folic acid supplementation do not follow international protocols; in pregnancy pathologies, screening is not performed in asymptomatic stages such as gestational diabetes and DHE4.

In Argentina, ninety percent of women receive care for institutionalized childbirth, however, ten percent arrive at delivery without having had contact with the health system, that is, without performing any prenatal control. Only 24.3% of women who are screened

start check-ups early in the first trimester (SIP-2008), and the number of women of childbearing age who were interested in preparing for pregnancy was lower5.

The World Health Organization advises that all women take folic acid supplements (400 micrograms of folic acid daily) from the time they decide to conceive a baby until 12 weeks of pregnancy. Women who have carried a fetus with a neural tube defect or have given birth to a child with this condition should be genetically counseled about the chances of it happening again, in addition to receiving high-dose folic acid supplements (5 mg daily) in the periconceptional period.)[6].

In recent decades, the association of HCI with vascular disorders has been a major issue. In one study, 11 of 58 severe EPs (19%) were found to have elevated homocysteine levels before 28 weeks' gestation. Pregnant women with preeclampsia have higher plasma homocysteine concentrations during the third trimester of gestation than healthy pregnant women. Compared to the control group, patients with preeclampsia have a higher frequency of hyperhomocysteinemia when they receive high doses of folic acid (5 mg folic acid daily)[7]. Hyperhomocysteinemia can increase the risk of developing peripheral vascular disease by making the blood vessels that supply the placenta more sensitive during pregnancy. Sensitivity can continue after pregnancy and increase the risk of vascular disease or coronary heart problems at any time in life. Some predictive risk factors for the development of PE before clinical presentation have been described8.

According to this background, it was observed that there are risk factors that are related to this pathology of pregnancy that have a high rate of MMP, but the etiological situation and the way to predict its development is not yet clear.

With the aforementioned background, we observed that there are many risk factors that are related to the development of PE, so we proposed to pose the following problematic situation.

Would *serum hyperhomocysteinemia be a predictor of preeclampsia in pregnancy*?

OBJECTIVE

To determine serum Hci levels in pregnancy from 12 to 20 weeks as a predictor of PE in patients attending the HUG, in the period from October 2018 to October 2019

JUSTIFICATION

Preeclampsia and eclampsia are a public health problem worldwide. The disease has no clear causes and several mechanisms have been studied to explain its appearance. Within these, elements have been found to have an increase in serum homocysteine or a

folate deficiency. Although the factors that cause high blood pressure are not fully understood, it is important to conduct research because of its importance to the health of the population. It seeks to provide up-to-date information and additional criteria in order to improve the assessment of the main risk factors influencing this disease, particularly diet, and to promote the relevance of antenatal visits and other preventive actions that will be very beneficial for women who are expecting a baby.

It is crucial to investigate this question because, according to the WHO's new model of antenatal care, the pregnant woman must have four to eight contacts with doctors throughout the pregnancy. Recent research indicates that an increase in the number of prenatal visits by women to the health system is associated with a decrease in the probability of deaths occurring in the prenatal period. This is because there are a greater number of opportunities to detect and address potential drawbacks. Prenatal care with at least eight visits can decrease perinatal mortality rates by as much as eight per 1000 births, compared to just four visits.

The research "HCI in pregnancy as a predictor of PE" was significant from a social point of view, since DUS are one of the main causes of maternal and fetal morbidity and mortality (MMF) in Ecuador. Currently, the cause of the pathology is not known, several studies have been carried out on the subject, but the definitive etiology and primary prevention techniques have not yet been identified, which would reduce MMF.

From the theoretical point of view, this study made it possible to know and confirm other risk factors for PE and helped to promote preconception care programs, thus being able to investigate ethological factors in a timely manner and carry out optimal prenatal control.

From a scientific point of view, this research provided one more procedure for the timely detection of DEU, as is the case with other biochemical and ultrasound markers that show the flow of the uterine arteries, as well as the early administration of aspirin and calcium during pregnancy.

From the methodological point of view, this information obtained was applied to the patients, timely diagnosing PE and its consequences; continue in future research related to the subject and include in the curriculum the programs for predicting DHE.

BACKGROUND OF THE RESEARCH

DUS dates back 3000 years, from ancient Egypt and China patients with seizures were reported; in the fourth century BC Hippocrates described these seizures as complications; In 1739, François Boissier de Sauvages introduced the word "eclampsia",

which originates from the Greek word "eclampsis", which denotes brightness, sparkle, glow or radiance, in order to distinguish eclampsia from other episodes of seizures that occur persistently and repetitively.

Pritchard first published on this hematologic condition in 1954, describing a case of patients with preeclampsia-eclampsia with erythrocyte destruction, thrombocytopenia, and hemostatic abnormalities. In 1982, Dr. Louis Weinstein Weinstein detected HELLP syndrome in pregnant women with hypertension, linking it to increased liver enzymes. MM is a serious health problem that causes 600,000 deaths annually globally, especially in developing countries, where the risk of maternal death is 1/48 compared to 1/1800 in developed countries1,9.

Eclampsia/PE occurs in 5 to 10% of pregnancies and is a major cause of death for both mother and infant. In addition, it causes prematurity, limitation in intrauterine growth, perinatal death, placental abruption and premature rupture of membranes due to maternal vascular disease, in addition to all the secondary repercussions of premature pregnancy, such as pulmonary and immunological immaturity. It occurs in about 12-22% of pregnancies and is the direct cause of 17.6% of maternal mortality in the United States10. Young women under 20 years of age are more likely to develop DHE, an age group in which the chances of suffering from triple syndrome11,12,48 are higher. The lack of general and particular health services, together with a high deficit in the self-care of the population's health. In Peru, Bryce and his team found that managing mild to moderate hypertension decreases the likelihood of unregulated hypertension, but does not prevent PE13.

In Germany, Beekers et al. found common complications between gestational diabetes and hypertension, with sensitivity and positive predictive values of 62-89% and 53-64%, respectively14. In South America, cases of DUS ranging from mild to severe have been reported, which are linked to depression, depressive symptoms, aggression, and a lower number of prenatal visits, with less than five, as psychosocial risk factors associated with PE15.

In one study, they observed that low-risk nulliparous women are willing to take aspirin in pregnancy and have high levels of acceptance as a preventive of PE. They also observed that aspirin use was associated with higher rates of vaginal bleeding16. Allotey et al. validated prediction models based solely on clinical features; clinical and biochemical markers; clinical and ultrasound parameters; and clinical, biochemical, and ultrasound tests that allowed the development and validation of the multivariate prediction model of PE17. There are a number of risk factors for PE that can be determined early in a woman's pregnancy18,19. Arterial hypertension, weight gain >0.85 kg/week, fetal growth restriction,

edema and decreased plasma albumin, thrombocytopenia, poor compliance, perinatal examinations, and tertiary hospital examinations were associated with severe PE.20 In a Swedish study about the direct causes of MM are dominated by hypertensive/PE disease, followed by thromboembolic disease, sepsis and obstetric bleeding21. The Japanese identified a total of 246 cases of eclampsia that corresponded to an incidence of 7.4/10,000 births with a mean age of onset of 30.7 ± 5.8 years. The proportion of primiparous women was 81.3%, and the mean gestational age at delivery was 36.7 ± 4.0 weeks. Four maternal deaths were identified in the PE group, which ranged from 8.6 to 27.8%[22]. Serrano et al. observed that women whose mothers had PE had a 3.38% higher risk than those who did not, and having an affected sister increased the odds of PE by 2. 95%[23].

In a study carried out at the Guasmo hospital in Guayaquil,24 high neonatal morbidity was found, with 58% of neonatal depression, 47% small for gestational age, 34% preterm and 25% with respiratory distress syndrome. Bajaña et al. found a correlation between the presence of DUS and PE25 in women aged 30 years and older. In Ecuador, the mortality rate is 21.1% per hundred thousand live births, which includes maternal deaths due to obstetric complications during pregnancy, childbirth or after childbirth. Eclampsia is the third most common cause of maternal death in the country, being responsible for 30% of cases. In a research carried out in Manabí, Ecuador, in 2016, it was found that 3.4% of the 3400 pregnancies had severe or moderate epilepsy, which has a significant impact on maternal and neonatal mortality, in addition to premature birth, decreased intrauterine growth, perinatal death and all complications linked to premature birth. such as pulmonary and neurological immaturity26.

In the last ten years, one study found that 11 out of 58 severe EPs (19%) had high Hci levels before 28 weeks gestation. This demonstrates the relationship between Hci and severe PE. Of the 289 subjects who developed PE after 28 weeks, 35 (10.4%) exhibited elevated concentrations of this metabolite. The increased sensitivity of the blood vessels in the uterus during pregnancy can continue after childbirth and increase the likelihood of developing vascular disease or heart problems in the future. This risk factor can contribute to the development of preeclampsia, as can a lack of folate or elevated levels of homocysteine in the blood. Some risk factors that predict the development of PD before clinical presentation have been described. Several studies related to the research topic support the research project presented.

Leeda et al. in 1998, studied the incidence of hyperhomocysteine in patients with PE, growth restriction with the effect of vitamin and methionine supplementation. A total of 207 patients with a history of PE or fetal growth restriction were evaluated, and Hci was

determined; 37 patients who had hyperhomocysteine were administered folic acid and vitamin B6, 27 had a second load of methionine and 14 patients became pregnant again with the use of vitamin and aspirin. All patients undergoing a methionine loading test after vitamin supplementation had a fully normalized methionine loading test. Of the 14 pregnancies that received aspirin and vitamins, 7 pregnancies were complicated with PE. They concluded that the administration of vitamin B6 and folic acid in patients with hyperhomocysteinemia prevents PE or growth restriction7

In 2001, Cotter Amanda et al. studied whether the determination of Hci in early pregnancy and the association with PE. Asymptomatic pregnant women in early gestation who later developed PE were evaluated. Hci was measured by polarized fluorescent immunoassay. Of the 56 patients studied with severe PE at 15.3 weeks and 112 controls at 14.9 weeks, Hci levels were significantly higher in PE, which concluded that early determination of hyperhomocysteine increases the risk of PE8

At the Sarda hospital, Secondi and his colleagues. We present a clinical case of a 30-year-old patient with severe PE and plasma Hci levels increased to 17.8 uml/l, with the normal value being less than 15. This finally triggered the termination of the pregnancy in the 28th week of gestation and the death of the baby. The findings support the importance of finding appropriate and available evidence for early detection of hyperhomocysteinemia. Unfortunately, the use of the hyperhomocysteinemia measure for this purpose is ineffective27.

Vargas et al. descriptively investigated HCI as a predictor of PE disease. According to the reviews carried out, it was possible to define the relationship between hyperhomocysteinemia and severe PE28.

In 2003, De la Calle and his collaborators. Hyperhomocysteinemia was examined in both groups by contrasting Hci levels in 50 pregnant women with fetal epilepsy (PE) against a control group of healthy pregnant women during the third trimester of gestation. A notable increase in homocysteine levels in the blood of individuals with preeclampsia was reported in contrast to the control group29.

Fernández et al. in 2005, studied the effect of folic acid and its relationship with plasma Hci levels in women who developed PE in the first and second trimesters of pregnancy, it was found that Hci values did not vary significantly with the administration of folic acid and that it did not influence the development of PE in the population studied3.

Hasanzadeh et al. In 2008, they studied the possible association between hyperhomocysteine and PE; 3 groups of patients were studied with the case control method 75 PE: mild, 37 with moderate PE and 38 with severe PE without complications in

pregnancy. The Hci was determined in all subjects. It is concluded that women who had PE had elevated Hci levels compared to those who did not have PE30.

Reina-Villasmil et al. in 2014 compared the plasma concentrations of HCI in PE, eclamptic and normotensive in the pre- and postpartum periods, in three groups of patients, the sample was collected before delivery and follow-up at 7 days and 6 weeks after delivery. The highest plasma concentrations were observed in the prepartum group of eclamptic patients followed by severe EPs. All groups had high HCI compared to controls, concluding that hyperhomocysteine is increased in eclamptics up to 6 weeks after delivery31.

In 2017, Maged et al. investigated the role of serum Hci and uterine artery doppler as predictors of placental complications such as growth restriction, PE, and other complications. In a prospective cohort study with miscarriage, 500 women were studied. HCI was taken at 15-19 weeks of gestation and Doppler was performed at 18-22 weeks of gestation. 453 patients completed the study, with women with uterine growth retardation and other complications than the control group, with significantly higher hyperhomocysteinemia and uterine artery resistance. Therefore, it was concluded that serum Hci screening and uterine artery Doppler would be good predictors of PE, intrauterine growth retardation, and other placental complications32.

Bhatia in 2017 studied the association of hyperhomocysteine with recurrent miscarriages in 50 patients who had miscarriages of unexplained causes. 19 cases had hyperhomocysteine of which 14 developed DHE, 47% of these had a low birth weight newborn compared to 25% of the control group; concluding that hyperhocysteinemia is associated with recurrent miscarriages and with a higher probability of developing PE and intrauterine growth retardation33.

Rasha et al. in 2018 studied the association between PE and plasma Hci levels in 61 pregnant patients; 30 normotensive and 31 with PE; it was found that hyper Hci was significantly higher in EPs than in normotensive ones34.

In a study conducted at the International Maternity and Child Health Hospital of Shanghai Jiao Tong University in 2017, Sun F et al. Hyperhomocysteine during the first trimester of pregnancy was found to be an independent risk factor for both gestational hypertension and severe gestational hypertension35. Mohini and his colleagues. In 2018, a study was carried out on the correlation between PE and Hci and folic acid levels; The study was conducted prospectively and used a control case of 50 patients with preeclampsia. Hci levels were found to be significantly high compared to the control group, while folate levels were low compared to the control group. However, the opposite was statistically insignificant. They found an inverse correlation between folate levels and Hci levels in pre-

eclamptic patients: Hci levels were significantly higher and folic acid levels were lower in Hci patients compared to the control group36.

Andrey et al. in 2018 carried out a systematic review to put together the available pieces of knowledge of Hci with pregnancy, they reviewed the articles from 1990 to 2017 of several databases (PubMed, ClinicalKey and Embase databases) in which they revealed that Hci levels are altered in uncomplicated pregnancy as in complicated ones, in some check-ups they tend to decrease in the second and third trimesters of pregnancy37.

Zarfeshan et al. in 2018, revealed a link between polymorphism and abortion. Sufficient data were obtained indicating the relationship between hyperhomocysteinemia and PE. Placental abruption was also associated with elevated Hci levels, increasing the risk of 5.3-fold, but there is still no data to support the hypothesis that Hci levels correlate with placental abruption38.

THEORETICAL BASES

The cause of DUS and PE has not yet been defined, but risk factors have been identified that play a role in their appearance. The review by Cruz Hernández (2018) analyzes the emerging risk factors for PE, which include biological phenomena such as oxidative stress, vitamin deficiency39 and endothelial dysfunction, among other immunological and endocrine aspects.

Another review by Paula J. Williams (2011), in which it is evident that some genes are predisposed to the occurrence and recurrence of PE. Research approaches involving the analysis of genes and connections in the relationship between the genotype of the fetus and the mother have been proposed. More than 70 potential genes have been investigated that are linked to a variety of pathophysiological processes, such as inflammation, the renin-angiotensin system, vasoactive proteins, thrombophilia and hypofibrinolysis, oxidative stress and lipid metabolism, endothelial injury. There are more than 20,000 genes and 10 million single nucleotide polymorphisms (SNPs), making many tests unnecessary. Placental anti-angiogenic factors are dysregulated and alter the endothelium, leading to an anti-angiogenic state with significant clinical outcome of PE. It is clear that PE has a genetic component, but this will depend on a complex genetic disorder and environmental factors40.

Biomarkers in maternal blood can predict PE early in pregnancy. Herraiz and Myatt showed that PE is predicted by a decrease in serum concentrations of maternal placental growth factor (proangiogenic) before 5 weeks and an increase in soluble forms such as tyrosine kinase1. However, the clinical utility of these biomarkers has not been evaluated in the studies carried out41,42. It is now known that women with PE have a placental disorder

that is characterized by an imbalance of angiogenic and anti-angiogenic factors. It was found that the serum concentration of placental growth factor (PlGF) decreased, while the concentration of tyrosine kinase 1 (sFlt-1) in its soluble form increased. And the onset of the disease is preceded by these altered values of PlGF and sFlt-141.

These placental metabolites predict adverse outcomes that occur within 2 weeks. The introduction of these biomarkers into clinical practice should be preceded by intervention studies.

Livingston et al. established that serum placental growth factor would be a predictor of PE, but this hypothesis was discarded with the studies carried out in which they established that this serum marker is decreased in the states of severe PE clinically demonstrated, but is not altered in the first trimester of pregnancy, which is why they considered it a poor marker to predict PE43.

In a multicenter study in the United States, Allen et al. found that risk factors, including angiogenic factors in maternal blood during the first and second trimesters, had a sensitivity of 88% and a specificity of 80% for predicting endometriosis in early pregnancy44. Poon et al. found that the combination of uterine artery Doppler in the late first trimester with placental growth factor and pregnancy-associated plasma protein (PAPPA) in maternal blood predicts early pregnancy with PE with a sensitivity of 93% and a specificity of 95%, but this model requires validation45.

A meta-analysis by Velauthar et al. demonstrated that Uterine Artery Doppler Echo in the first trimester had a sensitivity of 48% and a specificity of 92% in predicting PE. The prediction of endometrial disease is very accurate when a Doppler ultrasound of the uterine artery is performed at 20 weeks of gestation. In order to be used in clinical practice, it is necessary to validate all these models46.

Koopmans et al. investigated women with PE about the relationship between protein and creatinine in urine and suspicion of proteinuria. The protein/creatinine ratio is poorly understood and can be used in clinical practice. In conclusion, the protein/creatinine ratio of a single urine sample is a reliable indicator of renal dysfunction in patients with kidney disease. It may be an alternative rapid test method for the diagnosis of renal dysfunction47. Rojo and his collaborators. It was found that the usual production of nitric oxide (NO) is affected by enzymes, causing oxidative stress in the maternal and placental endothelia, with an increase in thromboxane A2 and a decrease in prostacyclin. These changes stimulate the Renin-Angiotensin system, resulting in an increase in peripheral resistance and generalized vasoconstriction. These modifications cause a decrease in the uterine flow of

the placenta, causing thrombosis in the placental vascular bed, fibrin accumulation, ischemia, and the formation of infarctions in the placenta48.

The circulating elements cause damage to the endothelial tissue, which leads to increased endothelial permeability, a reduction in the dilation capacity of blood vessels, and a decrease in the function that prevents platelet aggregation.

In one study, Gómez Jiménez et al. raised the connection between antiphospholipid syndrome (aPL) and epilepsy, especially when it occurs before 34 weeks of gestation. Lupus anticoagulant-dependent ACL (B2GPI) was found to be strongly associated with unfavorable pregnancy outcomes. suggests that pregnant women should generally perform a screening test with ACL-dependent Anti B2GP1. In patients with ACL who develop PE, endothelial damage may result from the release of vasoactive compounds, such as B2GPI, on the surface of the placental endothelium49.

During a 2017 Lapidus Alicia obstetrics congress, it was revealed that there are additional risk factors for endometrial disease, previous endometrial disease, hypertension in pregnancy, chronic kidney disease, high blood pressure, type 1 or type 2 diabetes, and autoimmune disorders, as well as moderate risk factors, such as first pregnancy at age 40. However, in clinical practice, only 30% of these factors predict the development of preeclampsia. Mean blood pressure at 15 weeks' gestation, birth weight, family history of coronary heart disease or heart disease, vaginal bleeding for more than 5 days during current gestation, and miscarriage with the same partner in less than 12 months are factors that predispose to heart disease in early pregnancy[50].

The clinical manifestations of the may be due to its maternal nature. Hypertension, proteinuria, and a fetal syndrome involving reduced fetal growth, reduced amniotic fluid, and fetal hypoxia, as well as systemic changes, are possible. Pregnant mothers who experience high blood pressure are more likely to suffer life-threatening complications, such as sudden onset of the normally inserted placenta, disseminated intravascular coagulation, brain hemorrhage, liver failure, and acute kidney failure. Nulliparous pregnant women with other complications or obvious risk factors are more likely to develop these complications, although preeclampsia is one of the most common types.

Therefore, hypertension is a pregnancy-specific syndrome that occurs in 3-5% of pregnancies and is diagnosed with increased blood pressure and proteinuria. A recent study revealed that hypertensive disease is more prevalent in pregnant women, with a rate of 7 compared to the predicted 10 cases. In 2010, INEC 2010 reported that the cause of maternal death in Ecuador was the leading cause. It is one of the main factors contributing

to maternal, fetal and neonatal mortality in underdeveloped nations and appears to be one of the main factors2.

The relationship between PD and mortality, as well as maternal and neonatal morbidity, demonstrates its clinical relevance. Pregnant women who do not receive PE treatment are at risk of developing serious complications such as eclampsia, liver rupture, stroke, pulmonary edema or kidney failure, which can be fatal51. In addition, PE is linked to preterm delivery and decreased fetal growth, either for iatrogenic or spontaneous reasons. Children born to mothers with epilepsy are at increased risk of developing bronchopulmonary dysplasia and cerebral palsy due to preterm and small-for-gestational-age births24,52,53. PE increases the risk of postpartum depression and quality of life54,55.

DHE are multisystems of unknown origin. These conditions include abnormal junction, hypoxia or placental ischemia, maternal endothelial dysfunction, and inadequate or excessive immune response, possibly due to immunogenetic abnormalities6. A wide variety of terminology and diagnostic criteria have been used over the years to classify DUS and define PE. Clinical manifestations of PE. The International Society for the Study of Hypertension in Pregnancy (ISSHP) updated the diagnostic criteria for PE in 2014. High blood pressure only after 20 weeks of pregnancy and associated with proteinuria (more than 300 mg/day) and other organic changes in the mother such as renal failure, hepatic, neurological, hematological involvement, as well as placental complications or fetal growth restriction are defined as PE.

There are two types of proteinuria: PE proteinuria and non-proteinuria. Blood pressure was measured in a seated and upright position or in the left lateral decubitus position with a manual or semi-automatic oscillometer certified for PE (Omron T9P or Omron MIT Elite devices)[56]. Hypertension is defined as a systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg twice in 4–6 h56. When women with underlying idiopathic hypertension have one or more of the above symptoms, they are diagnosed with PE. More aggressive treatment is recommended to prevent complications, as proteinuria is not an indicator of MM or MMP. The disease can present in a variety of ways, most often without symptoms, and is usually diagnosed during routine prenatal care. The findings indicate that 10% of women experience adverse effects; when the disease begins earlier, this risk increases to 15%[56].

Women who suffer from severe epilepsy report symptoms such as headaches, visual difficulties (including blindness), epigastric pain, nausea, and vomiting. Neurological problems include eclamptic seizures, a reversible ischemic stroke, cortical blindness, retinal detachment, and reversible encephalopathy. Liver dysfunction, bruising, or fractures are

signs of liver involvement, while renal involvement is characterized by acute kidney failure requiring dialysis. Cardiovascular manifestations include myocardial ischemia, infarction, and pulmonary edema. There is often bleeding and problems related to placental abruption and HELLP syndrome, which is characterized by microangiopathic hemolytic anemia, liver disease, and thrombocytopenia, without proteinuria, and heavy bleeding. HELLP syndrome is usually fatal, with a rapid deterioration of the mother's condition; A third of cases occur before 28 weeks of gestation. Growth restriction, prematurity with complications of preterm birth, fetal and neonatal death are examples of fetal complications. Because the clinical presentation of severe PE is heterogeneous, other disorders should be considered before definitive diagnosis.

In a 2011 systematic review by Thangaratinam et al., mean arterial pressure of 140 mm Hg or upper blood pressure of 170/110 mm Hg was found to be ineffective in predicting eclampsia, placental abruption, renal impairment, neurological impairment, and liver impairment (all of which are related to adverse maternal outcomes)[57]. After a diagnosis of illness (PE), blood pressure should be measured frequently or hospitalized, depending on the severity of the disorder. In general, medical history and physical examination assess the severity of PE and predict possible complications, but they are inaccurate and should not be used to make decisions about the management of birth behavior.

Laboratory tests . The urine protein/creatinine ratio is suspected of proteinuria in women with PE; There is little knowledge about the protein/creatinine ratio that should be used in the clinical setting as a measure of accuracy and prevalence, since they are varied56. Proteinuria does not signal immunosuppression specific to HELLP syndrome or site. Oxygen saturation anticipates detrimental maternal health outcomes in the first 48 hours after exposure. Monitoring of diabetic women includes biochemical examinations (liver and kidney) to assess progression and monitor the severity of the disease. These one-off tests are not effective in anticipating problems. Uric acid present in serum is an ineffective indicator of results and would not be evaluated in routine evaluation. If the platelet count is greater than 100 × 109 per L., the coagulation profile is not necessary. As a result, it is not considered a sensitive indicator of adverse coagulopathy.

Models for prediction. There were attempts to integrate these tests into multivariate models, but all of the tests mentioned have limited accuracy in predicting complications. Estimating overall risk is one way to assess the risk of adverse events among patients with PE.

To this end, predictive models have been developed that use predictors such as demographic characteristics, medical/birth history, symptoms and laboratory test results. A

combination of gestational age, chest pain or dyspnea, oximetry, platelet count, creatinine concentration, and aspartate transaminase (full PIERS model) can predict adverse maternal outcomes within 48 hours of the reminder of this disease59. The model's findings could be affected by the treatment paradox, where antihypertensive treatment or childbirth can reduce hypertension-related events such as stroke, eclampsia, and transient ischemic attack. The model could be affected by the drop in blood pressure.

Clinical management of PE. – Hospitalization for PE is recommended to avoid serious complications and consult with subspecialties in case of complications. It is recommended to avoid preloading by avoiding pulmonary edema and oliguria, which is not caused by fluid restriction or kidney failure. For severe hypertension during pregnancy, international guidelines recommend antihypertensive medications60. In 80% of women, in addition to magnesium sulfate, blood pressure can be monitored every 15 to 30 minutes Repeated doses of nifedipine, intravenous hydralazine, or labetalol should be given. The mother may benefit from treatment for maternal hypertension, which could affect the growth of the fetus without increasing the risk of fetal death.

Magnesium sulfate is the preferred drug for the treatment and prevention of eclampsia. Maternal risk assessment is the first management of PE, when fetal growth is limited, and induction/conduction is required. Work relationships reduce the risk of maternal high blood pressure, which reduces the risk of adverse outcomes for mother and baby. It also reduces the risk of cesarean section. Mechanical insemination using an exchange balloon or oral misoprostol is safer than traditional prostaglandins. Early delivery, either by induction or cesarean section, decreases the probability of negative results in women with non-negative DUS during weeks 34 and 37 of gestation56.

However, being born prematurely increases a baby's risk of developing breathing difficulties. Therefore, it is not justified to give birth immediately and the solution would be to maintain expectant vigilance until the clinical situation improves, which could be observed in the 37th week of gestation. Expectant management is often associated with an increased risk of placental abruption. Delivery in women with severe PE before 34 weeks is a topic of research, so expectant management is most appropriate in an equipped setting. Women with PE have been shown to have an increased risk of heart cardiovascular disease.

After childbirth, 30% of women experienced high blood pressure and 25% metabolic syndrome. Therefore, it is recommended that women who experienced complications during pregnancy such as gestational diabetes, intrauterine growth limitation, or preterm birth undergo cardiovascular disease risk assessments.

Thus, women with a history of PE are likely to develop microalbuminuria, something similar to patients with type I diabetes. According to some scientists, reducing heart disease after surgery and lifestyle modifications, such as physical activity, diet and smoking cessation, can reduce this risk by 4%. The American Heart Association advises that pregnant women with hypertension monitor their blood pressure, lipid profile, and blood glucose levels, as they may have a history of gestational diabetes and diabetes mellitus as risk factors for this disease.

Planning services and prevention of unwanted pregnancies are important strategies for reducing PE.

The fullPIERS model, an adaptation created to predict the risk of negative outcomes in these patients, should be evaluated at the time of admission of women admitted to hospital with impairment due to PE. Gestational age, headache, visual disturbances, chest pain, dyspnea, vaginal bleeding with abdominal pain, systolic blood pressure, and proteinuria strips are integrated into the model59

This comprehensive fullPIERS model was developed to predict maternal mortality or adverse effects of PE. The FullPIERS model does not include other negative results. As these findings may have short- and long-term adverse effects on maternal and infant health, their association with PE should be investigated.

Early PE lacks symptoms that would alert women to the need to seek medical attention. Regular and routine prenatal checkup, including blood pressure and proteinuria tests, are necessary for all pregnant women. The principle of increasing the frequency of visits in the last trimester when PE is more common in low-income patients. WHO recommends scheduling 4 basic antenatal visits in women at low risk of PE. Dietary calcium intake is poor in low-income strata. PE was less frequent in the Mayan Indians of Guatemala, who have a diet rich in calcium, which led to the hypothesis of the relationship between poverty and PE that would be given by calcium deficiency in diets. In populations with low dietary calcium intake, calcium supplementation in the second half of pregnancy has been shown to reduce PE62. The WHO recommends a daily dose of calcium of 1.5 to 2 g, which could be a limiting factor in patients with limited resources. In women at high risk of high blood pressure, the use of low doses of aspirin is recommended; Once high blood pressure is diagnosed, the mainstay of treatment is to control blood pressure, control delivery and placenta, and determine whether conservative treatment has more benefits from childbirth than conservative treatment.

In low-income countries, monitoring for hypertension, proteinuria, and early delivery care in critically ill patients could reduce maternal mortality from PE. Magnesium sulfate

reduces mortality, but it is not a cornerstone of MM reduction programs. Respiratory outcomes are not affected by prenatal exposure to corticosteroids after 34 weeks' gestation. An increase in infant mortality was observed in the general population, although no decrease in infant mortality was observed in low birth weight infants and in low-income groups. To reduce maternal and child mortality in low-income groups, health systems need to be reevaluated.

Prevention. Based on findings from individual patient data (IPD) in a meta-analysis, aspirin and other pharmacological drugs such as heparin and dalteparin demonstrated a moderate benefit for the prevention of PE in women at increased risk of PE, but trials have not reached definitive conclusions. PE correlates with a diet low in serum calcium. High-dose calcium supplements reduce PE, so women with a deficiency are advised to supplement with calcium (1.5 to 2 g daily) in the second half of pregnancy. According to a systematic review of calcium-rich supplements during pregnancy, cereals, such as wheat and maize, are the main source of calcium in the diet62. A randomized trial of women with PE testing the hypothesis that dietary calcium supplementation during early pregnancy can prevent PE. The presence of magnesium, vitamin C, and vitamin E in the diet does not reduce the risk of PE. Marine oil and other long-chain polyunsaturated fatty acids do not help prevent obesity.

Although only one randomized controlled trial was conducted to evaluate preventive vitamin D supplementation, vitamin D insufficiency was found to be linked to an increased risk of gestational diabetes, peptic disease, and low weight-for-gestational age. A combination of L-arginine and antioxidants was administered to women at high risk of PE with deficient synthesis of the nitric oxide precursor. Other studies in low-risk women routinely recommended L-arginine supplementation during pregnancy63. In response to lifestyle changes in primiparous women, a high intake of vegetables, fruits, and vegetable oils was associated with a lower risk of PD. In summary, aspirin therapy is the only way to prevent PD for which the evidence is strong, but the effects are not great. Other preventive interventions, except calcium supplementation in women with a low dietary calcium intake, require further evaluation and should not be prescribed without the context of clinical trials [62,64,65].

The daily intake of methionine is related to the amino acid homocysteine (Hci), which is obtained through transmethylation, remethylation and transsulfuration reactions66. This is based on the presence of vitamin cofactors such as folic acid, vitamin B12, and vitamin B6, which are essential for the enzymatic reactions of the enzymes methyltetrahydrofolate reductase (MTHFR), methionine synthetase (MS), and cystathionine beta synthetase

(CBS). In addition, mediators such as S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) are crucial to preserve balance if the concentration of Hci in plasma is increased.

It is present in vitamin cofactors such as folic acid, vitamin B12, and vitamin B6, which are essential for the enzymatic reactions of methyltetrahydrofolate reductase (MTHFR), methionine synthetase (MS), and cystathionine beta synthetase (CBS), as well as for defenders. Products such as S-adenosyl methionine (SAM) and S-adenosyl homocysteine (SAH), essential for altering balance, increase the concentration of Hci in plasma. If the balance is disturbed, there is an increase in plasma Hci levels, a situation known as hyperhomocysteinemia. It promotes various forms of cell development, thrombus generation, increased oxidative stress and cell apoptosis. Therefore, vitamin B12 and folic acid are essential for the metabolism of Hci.

A lack of these nutrients increases the concentration of Hci66. Endothelial cell dysfunction, including activator and inhibitor reactions, fibrinolytic systems, vascular cell matrix proteins, and vascular endothelial growth factors, resulting from hyperhomocysteinemia, affects the uterus-placental circulation. Changes in methionine-Hci metabolism were found to be linked to systemic vascular damage, which may be the typical clinical aspect of hypertensive disorders of pregnancy (THE). In addition, it is believed that elevated Hci levels may contribute to the development of placental microvascular diseases and endothelial diseases, which have a negative impact on the endothelium67.

Several studies have shown that women with severe PE are related to hyperhomocysteinemia68-70, but some authors oppose it and establish that the increase in homocysteine Hci in the second trimester is not related to PE, pregnancy-induced hypertension or fetal growth restriction71. According to previous studies and theoretical foundations, we observed that Hci is a thrombotic risk factor in patients with asymptomatic relatives, possibly related to folic acid in the diet. In addition, its association with the polymorphism of methyltetrahydrofolate reductase and its genetic, nutritional, oncological, psychological, bone metabolic and DUS effects is important.

LEGAL BASES

Various legal documents support the following research: *Homocysteine in pregnancy as a predictor of pre-eclampsia*

Constitution of the Republic of Ecuador

Article 3 dictates that the main obligations of the state are: "1. To ensure the effective enjoyment of the rights enshrined in the Constitution and in international instruments, especially in education, health, nutrition, social security and water for its inhabitants."

Article 32 establishes that health is a right that the State has the obligation to protect and whose fulfillment depends on the realization of other rights, such as access to water, food, education, physical training, work, social security, healthy environments and others that promote health. The State shall protect this right through economic, social, cultural, educational, and environmental policies, ensuring uninterrupted, timely, and unrestricted access to programs, actions, and services related to comprehensive health promotion and care, including sexual and reproductive health. Equality, universality, solidarity, interculturality, quality, effectiveness, efficiency, prevention and bioethics will be the rules that will guide the supply of health services with an emphasis on gender and age.

Article 48 establishes that the State, society and the family have the obligation to give priority to the integral development of children and adolescents, thus guaranteeing the full exercise of their rights. In all circumstances, the principle of the best interests of the child shall prevail and their rights shall override those of others. Article 3 states that the primary responsibilities of the state are: "1. To ensure the efficient use of the rights set forth in the Constitution and in international law, particularly in areas such as education, health, nutrition, social security, and water for its residents."

Article 386 establishes that the system will include programs, policies, resources and actions, merging with state agencies, universities, polytechnic schools, public and private research institutes, public and private companies, non-governmental entities and natural or legal entities that carry out research, technological development, innovation and those related to ancestral culture.

3. Ensure the dissemination of and access to science and technology, in addition to the use of discoveries and findings made in the context of the stipulations of the constitution and legislation.

4. To ensure freedom of creation and research within the framework of respect for ethics, nature, the environment and the recovery of ancient culture.

According to Article 388, the government will allocate the required funds for scientific research, technological progress, innovation, scientific education, the recovery and development of ancient knowledge and the propagation of knowledge. One element of these allocations will be used to fund projects through competitive funds. State-funded entities will be subject to the responsibility and monitoring of the relevant state72. Organic Constitution of Health

Article 6 dictates that all patients have the right to decide whether or not to access medical treatment. In both circumstances, the health centre has the obligation to inform him about the consequences of his choice73. Programme for the rapid reduction of maternal and neonatal mortality.

Article 1. Consider the National Plan for the Accelerated Reduction of Maternal and Neonatal Mortality, as well as the regulatory chapters that make it up, as a public policy of the first order for the health sector.

HYPOTHESIS

H1 Hyperhomocysteinemia in pregnant women between 12 and 20 weeks can provide timely prediction of the development of PE and other DHEs.

Ho Hyperhomocysteinemia in pregnant women between 12 and 20 weeks does not allow timely prediction of the development of PE and other DHEs.

SYSTEM OF VARIABLES

The theoretical concepts of the variables High blood pressure is a particular syndrome of pregnancy that occurs between 3 and 5% of pregnancies, and is diagnosed when the woman shows an increase in blood pressure, edema and proteinuria, factors that can cause MMF. The daily consumption of methionine has a relationship with Hci, an amino acid that is acquired through processes of transmethylation, remethylation and transsulfuration. The involvement of vitamin cofactors such as folic acid, vitamin B12 and vitamin B6 plays a notable role in PE-eclampsia74

It will be operationalized according to dimensions and indicators with: General characteristics and hypertensive states of pregnancy

SERUM HOMOCYSTEINE

The Hci will be operationalized according to dimensions and indicators with**:** Hci levels per laboratory <13 mmol/l (Reference value); Normal. High

EFFECTIVENESS

Specificity, sensitivity, and positive and negative predictive value

OPERATIONALIZATION OF THE VARIABLES

GENERAL OBJECTIVE: To determine serum homocysteine levels in pregnancy from 12 to 20 weeks as a predictor of PE in patients attending the University Hospital of Guayaquil Ecuador in the period from October 2018 to October 2019			
VARIABLES	**DIMENSIONS**	**INDICATOR**	
Serum homocysteine	Homocysteine levels by laboratory	5-13 µmol/L (Reference Value)	Normal Alto
	Specificity, sensitivity and positive and negative predictive value	75% 75%	
EP .	General characteristics Hypertensive states of pregnancy	Age Weight gain Parity: Origin: Antecedent of PE Instruction Blood pressure 120/80: mmHg: Protein in urine: Oedema:	Years Completed Starting weight, final weight Nulliparous, Primiparous, multiparous Rural, urban, dispersed Si, in the none, primary, secondary, higher normal/elevatedAbsent/present Absent/present

Vargas-Vera (2023)

MATERIALS AND METHOD

TYPE OF RESEARCH. This research work is prospective, longitudinal and correlational, with a non-experimental design because no variables were manipulated. It developed in different stages, until the birth of the product and the follow-up of the first weeks of the puerperium75

POPULATION. The study was carried out between October 2018 and October 2019 in a group of 6000 women who attended prenatal care at the maternal and child health department of the University Hospital of Guayaquil, located in the town of Guayaquil, in the Guayas region. The inclusion and exclusion criteria were applied to all pregnant women who attended antenatal care between 12 and 20 weeks' gestation. It was estimated that 25% of this group met the inclusion and exclusion requirements, which equates to approximately 1500 patients.

The study was conducted between October 2018 and October 2019 in a group of 6000 women who attended prenatal care at HUG's maternal and child health department. The inclusion and exclusion criteria were applied to all pregnant women who attended antenatal care between 12 and 20 weeks' gestation. It was estimated that 25% of this group met the inclusion and exclusion requirements, which equates to approximately 1500 patients.

SAMPLE. The formula was used to establish the random sample size. The prevalence of gestational hypertensive disease fluctuates between countries and provinces, even between provinces; however, it has been reported that the average prevalence in Ecuador is 8.29% with an accuracy of 0.05, which implies that a prevalence of 5 to 10% is

anticipated in Ecuador. Thus, the estimated proportion of each group was determined, which made it possible to assume that the data beyond this range were markedly different76.

$$n = \frac{N + Z2_x p_x q}{e2_x(N-1) + z2_x p_x q}$$

N = population size 6000

n = sample size confidence ?

Z= Level of 1.96

e= maximum estimate error 00.5%

p = probability of an event occurring 0.5

Q = probability that it will not occur 0.5

360 patients were selected for the study using the formula for an observational study, with a Zα value of 1.96 and a significance level of 95%. Patient Distribution – An Excel table of numbers with the random function was used to distribute patients in a simple, probabilistic random manner. All patients were monitored during pregnancy until the end of pregnancy for possible complications of hypertension.

INCLUSION CRITERIA

1. Patients in the second trimester of pregnancy who attended prenatal care when they were 12 to 20 weeks pregnant.
2. Patients who signed the informed consent to participate in the protocol.

CRITERIA FOR NON-INCLUSION

1. patients who had previous hypertension.
2. Heart disease
3. diabetes Millitus
4. persistent degenerative diseases.
5. Multiple pregnancies
6. Therapy with antifolic medications, such as methotrexate or antiepileptics.
7. Kidney diseases.
8. patients who are over 40 years old.

EXCLUSION CRITERIA

1. Patients who had not administered the drug adequately.
2. Not having your prenatal checkups.
3. Patients who concluded their pregnancy in a different medical entity.
4. Patients who did not participate in the research.

METHOD. Prior to informing the patient about the study, she was given a written informed consent to participate in the study, then the general data was taken by means of a medical history file validated by experts; 5 cc of peripheral blood was taken to determine the levels of Hci, which were processed in the laboratory

DATA COLLECTION. The information was extracted from the medical record and recorded on a form verified by specialists (see Annex 2A-B). The evaluation of Hci was carried out using a 5 ml sample of blood collected through a venipuncture. It was performed in the laboratory, performing a centrifuge at 4,300 revolutions per minute for 10 minutes at 4°C. The plasma (obtained from blood anticoagulated with EDTA) was segmented and then preserved in a plastic tube. He kept to himself. The Hci study was carried out using a turbidimetic method using Roche's COBA®6000 equipment with an analytical sensitivity of 0.5 µmol/L. The platform was COBA6000® able to carry out technical validations and reflex tests in real time. This test determined the level of Hci in the blood. Reference requirements: 5-12 µmol/L and an analytical sensitivity of 0.5 µmol/L.[77]

DATA ANALYSIS Version 20 of the SPSS program was used to analyze the results achieved, which were incorporated into a database defined in Excel 2010 (SPSS, Inc., Armon; NY)[78]. The qualitative variables were presented with their corresponding frequency and percentage distributions. Numerical variables were distinguished by their mean and standard deviation (SD), while variables that did not meet a normal distribution were distinguished by their median and interquartile range (IQR). Comparison of Risk Factors for DUS carried out by the University

A modification was made to a binary logistic regression model for each slope. This model was used to analyze the autonomous variables associated with each event. As with all polytomic variables, normal, low and high reference values were determined for numerical variables, with the aim of creating dummy variables.

RESULTS

In the present research "HOMOCYSTEINE IN PREGNANCY AS A PREDICTOR OF PRE-ECLAMPSIA" we will evaluate the results according to the objectives set

To determine the clinical and general characteristics in the first consultation of pregnant women from 12 to 20 weeks of gestation

In the first trimester of pregnancy, of the 312 women who attended the HUG obstetrics consultation, those with high blood pressure, cardiovascular disease, diabetes mellitus, current multiple pregnancy, treatment with anti-folates, detected kidney disease and who were over 40 years of age were not considered.

All variables, including risk factors for gestational hypertensive disease, together with sociodemographic variables (age, origin, residence, educational level, health service, etc.), and personal histories, whether pathological or not, showed uniformity. 58% of the patients lived in urban areas, 23% in rural areas and 19% in peripheral urban areas. The hereditary records of all the individuals studied were examined, including diabetes, hypertension, infertility, tuberculosis, cancer, heart, thyroid or kidney disorders, tobacco, alcohol and drug use, previous blood transfusions, allergies, intestinal diseases, gestational age, marital status, occupation, education, eating style, regular menstrual cycle and application of contraceptive procedures. 23.1% of the 72 patients had previously had more than two partners, which means a significant increase in blood pressure, both systolic and diastolic. The population analyzed showed similar characteristics in relation to their consumption of folic acid.

TABLE 1. Descriptive table (Initial homogeneity)

VARIABLE		**AVERAGE**
Age	19-year-old <	63(20.2%)
	> 35 years old	33(10.6%)
	20 – 34 years old	216(69.2%)
Starting Weight		65.64 + 15.01
Systolic TA		110 (66-144)
TA Diastólica		68 (44 - 98)
Weight gain		129(39.1%)
Proteinuria		21(9.1%)
Antecedent of PE	Yes	96 (30.7%)
	No	216 (69.3%)
Gestation	Primigesta	111(35.6%)
	Multiparous	201(64.4%)

Table 1 shows the initial homogeneity among the patients in the study in terms of age, weight, blood pressure, history of hypertension and number of pregnancies.

With respect to the risk factors studied, we observed maternal age, parity, low intake of foods rich in folate has an important value. See Table 2

To test Hci levels in pregnant women 12 to 20 weeks gestation.

Homocysteine values did not show significant values, of the 312 pregnant women only 9 patients (2.7%) had elevated serum homocysteine ranging from 12 to 15 IU, and 303 patients (84.5%) had normal homocysteine.

High homocysteine	9(2.7%)
Normal homocysteine	303(84.5%)

Relate Hci levels in the blood to the development of PE or some DHE. The proportion of DHE, the most important variable of interest, was not statistically significant (P 0.454), indicating a prevalence of 13.5% of hypertensive disease. Of the 312 pregnant women, 270 (86.5%) had a normal-evolutionary pregnancy, 27 (8.7%) had gestational hypertension, 9 (2.9%) had mild pelvic edema, and 6 (1.9%) had severe edema. In addition, 21 (6.7%) did not develop HELLP syndrome. Elevated serum homocysteine levels were not correlated with EHGs observed in pregnant patients.

TABLE 2. Risk Factors for Gestational Hypertension and Hypertensive Disease

VARIABLE		**PATIENTS (n312)**
Gestational age	< 15 weeks	141(56.6%)
	16-20 weeks	108(43.4%
Marital status	Common-law marriage	171(54.8%)
	Catholic	69(22.1%)
	married woman	72(23.1%)
Work	Student	42(14.3%)
	Housewife	162(55.1%)
	Other	90 (30.6 %)
Instruction	Primary	75(23.1%)
	Secondary	177(56.1%)
	Superior	60(19.2%)
Domicile	Rural	72 (23%)
	Urban	183(58.7%)
	Marginal urban	58(19%)
Gestations	Primigesta	108(46.4%)
	Multiparous	204(53.6%)
Couples	One	237(76.9%)
	More than two	75(23.1 %)
Folic acid intake	No	36 (11.5%)
	Preconception	57 (18.3%)
	Postconception	219(70.2%)

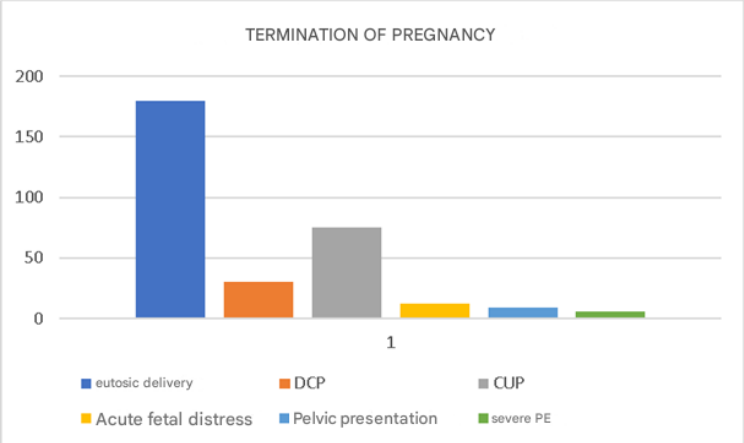
Foods rich in cereals and vegetables	No	0
	1-2 times	168 (53.8%)
	More than 3	144(46.2%)
Foods rich in meats	No	12 (3.8%)
	1-2 times	159(51%)
	More than 3	141(45.2%)
	normal	297(90%)
Table 3 shows a comparison of risk factors for hypertensive disease during pregnancy, with no notable differences between patients		

Table 3. EHG AND HOMOCYSTEINE.

Variable		Patients	%
EHG	Evolutionary norm	270	(86.5%)
	EHG	42	(13.5%)
EHG TYPE	Gestational hypertension	27	(8.7%)
	Lightweight PE	9	(2.9%)
	EP Severa	6	(1.9%)
Serum homocysteine (12.48)		9	(2.9%)
Proteinuria		21	6.7%

Perinatal data and the end of pregnancy All patients had an uncomplicated pregnancy and continued with regular prenatal check-ups, as well as the intake of iron, calcium and folic acid. 57.7% of pregnant women had a eutocic birth and 42.3% had a cesarean delivery, according to the results of the sample. The main reasons for cesarean section were: 30 patients (22.7%) due to pelvic narrowness, 75 (56.8%) due to a previous cesarean section, 12 (9.1%) due to acute fetal distress, 9 (6.8%) due to a pelvic product, and 6 (4.5%) due to severe PE**.** The mean weight of the newborns was 3227 g ± 407. (Graph 1)

Determine the efficacy of hyperhomocysteinemia using specificity, sensitivity, and positive and negative predictive values. Using the sensitivity of 80% and the specificity of 95%, we evaluated the positive and negative predictive value of homocysteine as a predictor of preeclampsia and found a positive predictive value of 44.7% and a negative predictive value of 98.9%. These results are related to the prevalence of preeclampsia in current research.



STATISTICAL ANALYSIS

To examine the results, we used two dependent variables: gestational hypertension and preeclampsia. A comparison was made between each of these variables with pregnant women with EHG and pregnant women without EHG; risk factors for EHG and PE have been considered independent associated variables.

The detailed study of 312 patients showed that 27 (8.7%) developed EHG and 15 (4.8%) developed PE. The group with hypertensive disease (n=42) and the group without hypertensive disease did not show statistically significant differences. This was attributed to risk factors such as age over 34 or under 20, excess weight or obesity, alcohol and tobacco use, and poor education. Only 30.8% of patients with a history of EHG had a personal history of PE, which proved to be statistically significant; however, only 2% of patients with no history of EHG had a personal history of PE; The patients who participated in the research were in the first trimester of gestation and required rigorous prenatal control until completion, which is why prenatal control was not considered a risk. When segmenting the population into three age categories, one from 19 to 19 years old, another from 20 to 34 years old, and the third from 35 years and older, we noticed statistically relevant variations in the proportions of gestational hypertension, mild pulmonary pathology, severe pulmonary pathology, and normal evolutionary pregnancies between each of the age categories.

Patients between 19 and 34 years of age showed normally evolving pregnancies in 85.7% and 88.9%, respectively, while in those over 35 years of age, the proportion of normally evolving pregnancies only reached 54.5%.

In addition, no significant difference was detected between individuals with severe PE. The percentages stood at 0%, 0.96% and 0.96% for individuals under 19 years of age, 20 to 34 years of age and 35 years of age, respectively (Table 4).

ANALYSIS OF THE PE VARIABLE

The detailed study of 312 patients involved notes that 15 (4.8%) of them experienced PE.

TABLE 4. Proportion of gestational hypertension in age groups

Pregnancy	< 19	20 - 34	> 35	Total
Normoevolutionary	54 (85.7%)	201 (88.9%)	15 (54.5%)	270
Hypertension Gestational	6 (1.92%)	12 (3.85%)	9 (2.88%)	27
Lightweight PE	3 (0.96%)	0 (0%)	6 (1.92%)	9
EP Severa	0 (0.0%)	3 (0.96%)	3 (0.96%)	6
Total	63	216	33	312

The levels of Hci in patients with PE and those with a normal pregnancy show Hci levels without statistical differences (p 0.0088) in patients with PE and (p 0.03766518) in patients with gestational hypertension (Table 5)

TABLE 5. Comparison of Homocysteine between patients with PE and normal pregnancies.

Variable	Gestational hypertension (n=27)	PE (n=15)	Evolutionary norm (n=297)
Homocysteine	10.05 ± 1.28	11.05 ± 1.29	10.13 ± 1.65

ANALYSIS OF THE RESULTS

DEUs stand out as the leading causes of MMP. It is widely recognized that they are linked to risk factors and it has been found in the literature that the extremes of female reproductive life are related to DHE19,25. However, our research did not detect women under 19 years of age or those over 35 years of age as risk factors. Clinicians' ability to anticipate PE before symptoms manifest has not progressed significantly in decades of study of the disease17,32,40

According to Guven et al. (2009), during the third trimester, Hci levels are higher in patients with preeclampsia compared to healthy pregnant women. Thus, Hci levels could be used as an indication of preeclampsia3,7,8,9,27,29,31-33-35,37. These levels are considered to cause endothelial dysfunction and intrauterine growth delay66,68,69; however, this study did not detect an increase in these levels; in contrast, Hci levels in PE patients were within normal ranges. According to Sun research, hyperhomocysteine during the first trimester is an independent risk factor for severe PE36.

Other studies also report elevated levels of Hci in early pregnancies, linking them to the later emergence of mild PE7. Kharb et al. found that Hci levels in the maternal blood of pregnant women with hypertension were slightly higher compared to pregnant women with normotensive hypertension ($p < 0.001$, $p > 0.05$ respectively). Vitamin B12 levels in the maternal blood of hypertensive pregnant women were lower compared to normotensive pregnant women, suggesting that folate and vitamin B12 deficiency, together with high Hci levels during pregnancy, may be a risk factor for lung disease and future cardiovascular risk50. However, our findings do not align with these publications, as Hci levels did not show a direct correlation with the development of PE as a result of a folic acid-enriched diet, in addition to supplementation of 5 mg of folic acid since the patient joined the study.

Maged et al. concluded that serum ICH screening and uterine artery Doppler would be good predictors of PE, intrauterine growth retardation, and other placental complications32. This was not corroborated in our study because the uterine arteries were not Doppler performed on our patients.

Mujawar et al. demonstrated that, in pre-eclampsia, serum Hci, folic acid, and vitamin B12 levels are altered81; and hyperhomocysteinemia and low folic acid levels are related to PE6,27,82. However, some studies, such as the one published by Wadhwani et al., evaluate the levels of maternal plasma folate, vitamin B12, and Hci in women with normotensive control (CKD) and women with PE from early pregnancy to delivery83. At all times, maternal plasma homocysteine levels were higher in PE than in CKD. These findings contradict those of current research and suggest that women with PE have higher levels of homocysteine from early pregnancy to delivery. In this context, our research has found no evidence to suggest folic acid supplementation to decrease the possibility of PE and minimize homocysteinemia levels84. Thus, we can contrast our results with those that Mujawar et al.[81] published in 2011, which indicate that Hci concentrations in the blood have a negligible negative correlation in patients with PE85. Hci levels vary in both uncomplicated and complicated pregnancies, and according to some reviews, they tend to be reduced in the second and third trimesters of gestation, according to Andrey et al.[Question 37].

Sociodemographic and cultural elements have a considerable influence on folate consumption86-89. Since 1996, both Mexico and Chile have included folic acid in flour as a component of the neural tube closure abnormality prevention program. This is a component of the basic nutrition program in Mexico and in several Latin American countries. In the United States, 20% of the population does not consume folic acid supplements and its incidence is comparable to that of the rest of the population, supporting the idea that folic acid levels do not affect the progression of PE9. Currently, it is known that

hyperhomocysteinemia represents a cardiovascular risk, causing endothelial damage in veins and arteries due to a decrease in the capacity to absorb deoxyuridine47,56, including the placental vasculature. Therefore, it is crucial to consider higher doses of folic acid during pregnancy to prevent the emergence of preeclampsia66,90. Folic acid L-arginine supplementation may help prevent PE by enhancing endothelial function91.

Pregnant women show evidence of hyperhomocysteinemia as a predictive factor for PE; however, our research found no significance due to their meals being enriched with folic acid; this indicates that exogenous folic acid intake does not have a significant impact on the progression of PE. This provides us with a scheme for randomized, blinded, and placebo studies, which allows us to establish the dose and its relationship with PE. The daily recommendation for folic acid to reduce the risk of neural tube closure abnormalities is 1 to 5 mg91.

According to Briceño and Briceño92, there are numerous studies that seek to clarify the cause of the various DUS in pregnancy and establish timely prevention and cure. In addition, it is necessary to choose patients correctly and take into account the severity of mothers and fetuses, starting with inducers of lung maturation, administering antihypertensives, magnesium sulfate and monitoring the progress of the fetus.

As has been demonstrated, DUS is one of the main causes of MMP, showing a notable chronic disability and death in mothers. In addition, they lead to serious and relevant problems in the newborn, such as premature birth, delayed intrauterine development and loss of the placenta. Prevention or treatment methods have not been developed for these disorders3,19,24,25. A health priority should be the reduction of maternal and fetal complications caused by DHE. It is estimated that in Ecuador alone, 43 deaths from this reason were registered in 2013, with a projected maternal mortality rate of 43 per 340,000 live births94.

In Argentina, only 24.3% of women of childbearing age expressed interest in preparing to undertake pregnancy during the first trimester (SIP - 2008), and check-ups begin early in the first trimester5. In contrast, the incidence of PE, whether mild or severe, varies between 5 and 8%, or even 10%, with a significant rate of maternal and fetal mortality, in addition to prematurity, intrauterine growth delay, and placental abruption95,96 . The percentage incidence of DUS found in this study was 13.5%, something similar to that reported in previous studies. The corresponding proportion stood at 8.7% for gestational hypertension, 4.8% for distributed hypertension, 2.9% for mild hypertension, and 1.9% for severe hypertension. No significant variations were observed between sociodemographic, personal, pathological, and gynecological-obstetric risk factors (p 0.0088), nor among what

was published in the literature94. The danger of the disease recurrence is linked to the history of previous PE.

A recurrence of 25 to 65% has been reported in patients with severe prior PE and 5 to 7% in patients with moderate prior PE; this information contrasts with the frequency of less than 1% in patients with previous normal EP. In our research, five patients had PE and had a history of PE; this constitutes 40% of the patients and 25% had gestational hypertension, findings that are similar to those reported by other authors97.

There are multiple studies that have examined modifications in the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in the metabolism of homocysteine, an intermediate sulfur amino acid of methionine metabolism, from food proteins. Substitution of C for T in nucleotide 677 (C677T) modifies serum homocysteine levels, which could represent a risk factor for PE. This mutation has been found to be related to higher Hci levels in patients with severe PE, in contrast to patients with mild PE and control groups98-99

Chedraui et al. determined the prevalence of C677T and A1298C single nucleotide polymorphisms (SNPs) of the *MTHFR gene* in nulliparous women complicated with PE and concluded that the prevalence of the CC mutant genotype of the A1298C polymorphism was higher in women with eclamptics67. Likewise, the same authors determined the frequency of the C677T and A1298C SNPs of the MTHFR gene in the placenta of PE pregnancies and healthy controls, and observed that the frequency of the TT mutant genotype of the C677T polymorphism was higher in the placenta of pregnancies complicated with pre-eclampsia100. In our research it was not possible to determine this genetic polymorphism.

The research had certain restrictions. Initially, we propose to increase the volume of the sample. It was found that high doses of folic acid did not decrease the PE index, and an opposite trend was detected, in which higher proportions of hypertensive disease were recorded during pregnancy, although not statistically significant. We are convinced that the result is attributed to the first restriction established, so it is recommended to carry out an analysis to find analogies with hypertensive conditions during pregnancy. In 2015, Ochoa discovered that MTHFR mutations are the same as those mentioned in the literature9.

CONCLUSIONS

Finally, since eclampsia and PE represent the second most frequent cause of maternal death globally, hypertensive disorders during pregnancy are a public health issue.

By studying the clinical and general features of pregnant women in the first consultation during the 12th and 20th week of gestation, we have been able to verify that

the risk factors for DUS were found in the population studied. All sociodemographic variables (age, origin, residence, educational level, medical service, etc.), as well as personal histories, both pathological and non-pathological, demonstrated uniformity as risk factors for gestational hypertension.

Regarding their origin, 58% of the patients came from urban areas, 23% from rural areas and 19% from peripheral urban areas. In addition, they had a family history related to diabetes, hypertension, infertility, tuberculosis, cancer, and heart, thyroid, or kidney disorders. In addition, they had tobacco, alcohol and drug use, previous blood transfusions, allergies, intestinal pathologies and surgeries. 23.1% of patients had had more than two previous partners, which turned out to be statistically relevant for systolic blood pressure.

86.5% of pregnant women experienced a normal evolution of their pregnancy, 8.7% showed gestational hypertension, 2.9% experienced mild pregnancy problems, and 1.9% experienced severe pregnancy. A statistically significant HELLP syndrome (P 0.454) was not observed, which is aligned with a prevalence of 13.5% of hypertensive disease during pregnancy and 4.8% for PE. Homocysteine levels in pregnant women aged 12 to 20 weeks did not present statistical variations in patients with hypertensive disorders of pregnancy; that is, when serum homocysteine levels were linked to the onset of PE or hypertensive disorders of pregnancy; both patients with PE and those who experienced a normal evolutionary pregnancy did not present statistical differences.

We examined the effectiveness of hyperhomocysteinemia as a marker of preeclampsia by using specificity, sensitivity, and positive or negative predictive value. With a sensitivity of 80% and a specificity of 95%, a positive predictive value for preeclampsia of 44.7% and a negative predictive value of 98.9% were recorded, which would be adjusted to the prevalence of preeclampsia in existing studies. Therefore, we conclude that serum hyperhomocysteinemia is a predictor of PE during pregnancy and that early administration of 5 mg of folic acid does not reduce the risk of hypertensive alterations during pregnancy; that in our research, the prevalence of hypertensive diseases was 13.5%; that our findings did not show a correlation between serum homocysteine levels and the birth of the Finally, no statistically significant differences were detected between the proportions of hypertensive gestational pathology and normal evolutionary pregnancy in these patients; Approximately 87.3% of patients in the category of patients under 35 years of age suffered a normal evolutionary pregnancy, while this percentage rose to 90.9% in the category of patients who exceeded 35 years of age. On the other hand, this percentage rose to 90.9% in the category of patients who exceeded 35 years of age.

RECOMMENDATIONS

This research seeks to prevent hypertensive disorders of pregnancy and preeclampsia in particular; Based on individual patient data findings, aspirin is the drug of choice for preventing preeclampsia; It is important that the Faculties of Medical Sciences and Medical Careers are empowered in this field of prevention of hypertensive disorders of pregnancy, since it is one of the main causes of maternal death. To evaluate the possible risks for this vulnerable group of women who are prone to develop this pathology, the MSP and doctors program promotion and education campaigns on preconception care, prenatal control.

The outcome of this study made it easier for us to make progress in understanding some of the possible risk factors for hypertensive disorders of pregnancy, in which the most susceptible people are young people and individuals aged 35 years and older. The discoveries will provide us with the possibility of promoting actions for the prediction and prevention of hypertensive disorders during pregnancy. This will facilitate future studies with other population groups and samples with more patients, in addition to the involvement of other participants in the research such as the faculty of medical sciences, educational sciences, journalism, among others.

In a meta-analysis, it was shown that aspirin, together with other substances such as heparin and dalteparin, favor women at risk of preeclampsia 101, 102, and multiple studies support the prevention of hypertensive alterations during pregnancy with aspirin. Thus, diet and low levels of calcium in the blood are often linked to PE. Calcium supplementation is advised during the second half of pregnancy (1.5 to 2 g per day), as supplements containing large amounts of calcium decrease PE. Cereals, such as wheat or corn101,102, are one of the most significant sources of calcium in the diet. Weight loss during early pregnancy can be prevented through dietary calcium supplementation. This is corroborated in a randomized study of women with a history of physical activity. A diet rich in vegetables, fruits, and plant-based oils was found to decrease the risk of preeclampsia.101-102 In conclusion, the only method to avoid PE is the use of aspirin. To suggest other preventive measures, additional research is needed.

Homocysteine is related to daily methionine intake and interacts with the enzymes methyltetrahydrofolate reductase (MTHFR), methionine synthetase (MS), and cystathionine synthetase (CBS). An increase in homocysteine levels occurs in the plasma, a condition known as hyperhomocysteinemia. This increase has an impact on cell proliferation, thrombus generation, increased oxidative stress and cell apoptosis. Folic acid and vitamin B12 are essential for homocysteine. The absence of folic acid causes an increase in the

amount of homocysteine. The common clinical presentation is due to systematic vascular damage associated with changes in methionine-homocysteine metabolism. Hyperhomocysteinemia alters the operation of the vascular endothelium, activating and inhibiting fibrinolytic systems, cell matrix proteins, and vascular endothelial growth elements.

Finally, based on the studies carried out and the theoretical basis, we observe that homocysteine is a risk factor for thrombotic and hypertensive disorders of pregnancy that is related to a deficiency of folic acid in the diet or in supplementation. However, our study did not conclude that hyperhomocysteine is a predictor of preeclampsia, so it is important to recommend a diet rich in folate and folic acid.

Accessibility to high-quality family planning services and prevention of unwanted pregnancy are important strategies for reducing PE. Significant progress has been made in smartphone-based systems that enable prediction of PE risk in low-resource strata using algorithms based on simple clinical data using or without a smartphone with pulse oximeter. The miniPIERS model, an adaptation of the PIERS model, is used to assess women admitted to hospital with impairment from PE at the time of admission. This model was created to predict the risk of negative outcomes in these patients. The model integrates factors such as gestational age, headache, visual disturbances, chest pain, dyspnea, vaginal bleeding with abdominal pain, systolic blood pressure, and proteinuria strips59.

Women do not show symptoms that alert them to the need for medical attention when they experience early sex education. All pregnant women should receive regular and routine prenatal checkups, including blood pressure and proteinuria tests. the principle of increasing the frequency of visits in the last trimester, when PE is present in low-income patients. WHO recommends scheduling four basic antenatal visits for women who are at low risk of developing PE. Low-resource groups have a low intake of dietary calcium. PE was less common among the Maya Indians of Guatemala, who have a diet rich in calcium, leading to the hypothesis that PE and poverty are related by calcium deficiency in diets.

In populations with low dietary calcium intake, calcium supplementation in the second half of pregnancy has been shown to reduce PE62. The WHO recommends a daily dose of calcium of 1.5 to 2 g, which could be a limiting factor in patients with limited resources. Compared with placebo, low-dose calcium supplements (usually 500 mg daily) consistently decreased PE in a review of randomised trials. In women at high risk of preeclampsia, the use of low-dose aspirin is recommended; once preeclampsia is diagnosed, the mainstay of treatment is to control blood pressure, management of delivery and placenta, and to see if the benefits of delivery are greater than conservative treatment

In low-income countries, monitoring for hypertension, proteinuria, and early delivery care in critically ill patients could reduce maternal mortality from PE. Magnesium sulphate reduces mortality, but it is not the main component of programmes to reduce maternal mortality. Respiratory outcomes are not affected by prenatal corticosteroid exposure after 34 weeks' gestation. In low-resource nations, monitoring of high blood pressure, proteinuria, and early delivery care in patients with severe illness could decrease maternal mortality by childbirth. Magnesium sulphate reduces mortality, however, it is not the essential element of programmes to reduce maternal mortality. Exposure to antenatal corticosteroids after 34 weeks' gestation has no impact on respiratory outcomes. There was an increase in neonatal mortality in the general population, although there was no evidence of a decrease in neonatal mortality in low birth weight newborns and in low-resource areas. To reduce the MMP, by PE in the strata of limited resources, it is necessary to review the health systems.

Prevention. Based on individual patient data (IPD) findings from a meta-analysis, aspirin and other pharmacological drugs, such as heparin and dalteparin, offered moderate benefits for the prevention of PE in women at increased risk of PE. However, trials have not reached definitive conclusions. PE correlates with a diet low in serum calcium. High-dose calcium supplements reduce PE, so women with a deficiency are advised to supplement with calcium (1.5 to 2 g daily) in the second half of pregnancy.

According to a systematic report on supplements containing large amounts of calcium during pregnancy, cereals are the main source of calcium in the diet. A randomized study in women with PD is testing the hypothesis that adding calcium to the diet during early gestation could prevent PE. The inclusion of magnesium, vitamin C and vitamin E in the diet does not reduce the risk of lung disease. Marine oil or other polyunsaturated long-chain fatty acids do not contribute to the avoidance of PE.

Although only one randomized controlled study was conducted to assess preventive vitamin D supplementation, a lack of vitamin D was found to be associated with an increased risk of gestational diabetes, peptic diseases, and low weight-for-gestational age. A mixture of L-arginine and antioxidants was implemented in women at high risk of PE, using the precursor nitric oxide with insufficient synthesis. Some research conducted in low-risk women suggests regular L-arginine supplementation during pregnancy63. In response to lifestyle changes, nulliparous women who ate diets rich in vegetables, fruits, and plant-based oils were found to have a reduced risk of PE

In summary, aspirin treatment is the only way to prevent PE that has strong evidence, but its effects are not significant. Other preventive interventions, except calcium

supplementation in women with a low dietary calcium intake, require further evaluation and should not be prescribed without the context of clinical trials62,64,65.

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