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Original article

The Association between 4-Hydroxyglutamate and Pre-Eclampsia

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SUMMARY

Introduction/Aim. Pre-eclampsia is a major cause of perinatal mortality. Glutamate plays a critical function in the promotion of a healthy pregnancy. Therefore, the aim of this study was to determine the extent of the correlation between pre-eclampsia and 4-hydroxyglutamate acid.
Methods. This is a case-control study that was conducted on a sample of 100 pregnant women in the third trimester. The study group consisted of 26 cases of mild pre-eclampsia and 24 cases of severe pre-eclampsia, while the control group consisted of 50 normotensive pregnant women. In addition to human 4-hydroxyglutamate, which was measured by ELISA, liver function test, renal function test, uric acid, serum lactate dehydrogenase (LDH), complete blood picture, and urine albumin were performed for all patients.
Results. The mean level of 4-hydroxyglutamate was significantly higher in the case group (mean ± SD = 243 ± 59 pg/ml) than in the control group (mean ± SD = 90 ± 45 pg/ml), with a range of 29–351 pg/ml vs 4–185 pg/ml and a p-value of < 0.0001/ml. Severe pre-eclampsia patients had higher mean 4-hydroxyglutamate levels (257.88 ± 43.436 pg/ml) than mild cases (229.77 ± 68.789 pg/ml), although the difference was non-significant. A 4-hydroxyglutamate level of ≥ 142.5 was shown to be a highly sensitive (92%) and specific (85.2%) indicator of pre-eclampsia using the receiver operator characteristics curve. A 4-hydroxyglutamate level of ≥ 142.5 led to a 5.75-fold higher risk of pre-eclampsia.
Conclusion. The level of 4-hydroxy glutamate was increased significantly in pregnant women with pre-eclampsia compared to healthy women and could be used as a predicting marker with high sensitivity.

Keywords: **pre-eclampsia, glutamate, laboratory markers**

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INTRODUCTION

Glutamate and glutamine are amino acids that are substantially consumed and highly prevalent in the neonate during the final phases of gestation. Glutamine is involved in the metabolism of carbon and nitrogen in fetuses and has a significantly higher concentration ratio in the plasma of fetuses than in their mothers, surpassing other amino acids in humans and mammals (1).

Pre-eclampsia (PE) is often regarded as a placental disorder since it manifests in individuals with hydatidiform moles and the only effective treatment is the delivery of the placenta. Effective implantation of the embryo and the subsequent development of the placenta requires proper spiral arteries remodeling via trophoblastic invasion. Emerging evidence indicates that an insufficient energy supply may result in abnormal implantation and superficial spiral artery remodeling, which disrupts the metabolome of the placenta and fetus. This disruption can lead to placental ischemia-induced pre-eclampsia, which is followed by pervasive alterations in the metabolome. Therefore, PE is linked to many metabolic problems such as dyslipidemia, hyperuricemia, hyperglycemia, and insulin resistance (2–4). It is widely accepted that the regulation of glutamate and glutamine transfer in the placenta is essential for the success of a healthy pregnancy (5).

The function of glutamate in the PE has not been thoroughly examined. Sovio et al. (5) found that when measured in the first trimester, it could serve as a reliable predictor of the occurrence of pre-eclampsia. In this study, we aimed to determine the association between 4-hydroxyglutamate acid and pre-eclampsia in the third trimester.

PATIENTS AND METHODS

This research is a case-control study carried out at the Department of Obstetrics and Gynecology of Baghdad Teaching Hospital during the period between February and October 2022. Administrative approvals were granted from the Council of Iraqi Board of Medical Specialization: registration number (EAC–1248) on January 5, 2022. Also, the approval of the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital was obtained: registration number (8557) on December 21, 2021.

The study included a sample of 100 pregnant women in the 3rd trimester ≥ 28 weeks of gestation. The women were divided into two groups. Group 1: The case group consisted of 50 pregnant women with pre-eclampsia, with 26 cases being mild and 24 cases being severe. Group 2: The control group consisted of 50 normotensive individuals.

The inclusion criteria for study groups were singleton pregnancy in the third trimester (28 to 39 weeks) with pre-eclampsia in mild or severe form with a viable fetus. Women with gestational age less than 28 weeks, and those with chronic diseases (chronic hypertension, diabetes, thyroid disease, renal disease, liver disease, autoimmune disease, hematological diseases, cardiovascular diseases), multiple pregnancies, smoker, chronic drug users, eclampsia at presentation, intrauterine fetal death were excluded from the study. All patients were informed about the nature of the study and verbal consent was taken from them.

Patients in both groups underwent general examination, vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, body temperature) were checked as well as abdominal and obstetric examination. A mercurial sphygmomanometer was employed to measure the blood pressure (BP) after the patient had been seated for a period of time. In the event that the measured BP was 140/90 or higher but less than 160/110, the BP would be reassessed after approximately four hours. A urine sample would be collected to test for albumin if the reading remained the same or increased. The patient would be diagnosed with pre-eclampsia and enrolled in the study if the result was positive. For those with BP of ≥ 160/110, a urine sample for albumin would be requested without delay and when positive, the patient would be confirmed with pre-eclampsia. Subsequently, a blood sample would be collected. The level of S. 4-hydroxy-L-glutamic acid was performed for all patients in addition to other laboratory investigations such as proteinuria, protein/creatinine ratio, liver function test (AST, ALT, S. albumin), complete blood count (CBC), uric acid, LDH, renal function test (BUN, S. creatinine).

Demographic and clinical data were collected through the distribution of a well-designed questionnaire including maternal age, educational level, occupation, residency, parity, and gestational age, which was confirmed by early pregnancy ultrasound as well as abdominal and obstetrical ultrasound (Philips HD 11 ultrasound machine) performed by a radiologist at the time of admission.

Blood sample collection: Five milliliters of venous blood were obtained from the participants prior to the administration of any medication. The entire blood sample was collected with anticoagulant containing tubes, such as citrate or EDTA. The tubes were centrifuged at a speed of 2,000 to 3,000 rpm for 20 minutes after being maintained at ambient temperature for a period of 10 to 20 minutes. Retrieved plasma samples were frozen at -4 °C and thawed prior to measurement.

Human 4-hydroxyglutamate (4OHGlu) was measured using a designated ELISA Kit Catalogue Number: SL3706Hu) and loaded into the analyzer. The assay range provided by the manufacturer is 4 pg/ml-200 pg/ml

Statistical analysis: All statistical analyses were conducted using IBM-SPSS (USA Chicago) and data were presented in the form of counts, percentages, mean, standard deviation (SD), minimum (Min), and maximum (Max).

The association between categorical variables was assessed by Chi-square or Fisher exact test, while the Student's t-test or Mann-Whitney u test was used to compare continuous variables, as suitable. The receiver operating characteristic (ROC) curve was utilized to determine the optimal cut-off points, following the Yoden J index test, for estimating the area under the curve (AUC), sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), test accuracy (Acc), and relative risk of each variable.

RESULTS

The demographic data of study groups are illustrated in Table 1. There was no significant difference between the study and control groups.

The case group had significantly more irregular antenatal care visits, although there was no statistically significant difference between educational level and residency, as shown in Table 2.

As depicted in Table 3, both baseline systolic and diastolic blood pressures were significantly higher in the case group compared to the control group. Further, investigations showed that the values of liver function test were significantly higher in the study group as compared to the control.

Table 1. *Demographic data*

Variables	Case		Control		P Value
	Mean	SD	Mean	SD	
Age	29	9	28	8	0.508
Gravidity	4	3	5	3	0.268
Parity	2	2	3	2	0.233
Miscarriage	1	1	1	1	0.789
GA	33	7	34	7	0.409

* GA: gestational age

Table 2. *Antenatal care, education distribution*

Variable		Case	Control	Total	P value
		No. (%)	No. (%)	No. (%)	
ANC (antenatal care)	**Irregular**	47 (94)	33 (66)	80 (80)	**< 0.0001**
	Regular	3 (6)	17 (34)	20 (20)	
Educational level	**Illiterate**	10 (20)	14 (28)	24 (24)	0.106
	Primary	19 (38)	24 (48)	43 (43)	
	Secondary	14 (28)	11 (22)	25 (25)	
	University	7 (14)	1 (2)	8 (8)	

*ANC: antenatal care; No.: number

Table 3. *Distribution of vital signs and relation between different parameters in studied groups*

Variables	Case		Control		P value
	Mean	SD	Mean	SD	
Systolic BP	158	22	126	12	**< 0.0001**
Diastolic BP	97	21	68	15	**< 0.0001**
PR	94	25	92	24	0.689
Variables	Control		Mild	Severe	P value
	Mean ± SD		**Mean ± SD**	**Mean ± SD**	
AST (aspartate transaminase)	38.04 ±9.52		76.15 ±24.51	86.88 ±22.43	**< 0.0001**
ALT (alanine transaminase)	37.92 ±9.91		78.58 ±21.08	92.25 ±21.07	**< 0.0001**
BUN (blood urea nitrogen)	21.78 ±5.38		27.58 ±3.74	28.83 ±4.33	**< 0.0001**
Creatinine	1.25 ±0.34		1.85 ±0.19	1.89 ±0.22	**< 0.0001**
Uric acid	5.82 ±0.93		6.94 ±0.82	6.95 ±0.89	**< 0.0001**
S. albumin	3.85 ±0.47		3.14 ±0.41	3.28 ±0.49	**< 0.0001**
LDH	178.74 ±34.65		260.58 ±46.17	284.38 ±47.58	**< 0.0001**
Platelet	258.26 ±66.79		93.46 ±17.84	89.46 ±16.8	**< 0.0001**
Protein/Creatinine ratio	21.84 ±4.4		35.95 ±4.69	34.87 ±4.88	**< 0.0001**

*BP: blood pressure; PR: pulse rate; *n= number, *SD = standard deviation, *P = probability, *AST = Aspartate transaminase, *ALT = Alanine transaminase, *BUN = Blood urea nitrogen, *S = serum, *LDH = Lactate dehydrogenase, *Cr = Creatinine

Table 4. *Distribution of 4-hydroxy glutamate*

	Mean	Standard deviation	P. value
Case	**243**	**59**	**< 0.0001**
Control	**90**	**45**	**< 0.0001**

Table 5. *Distribution of 4-hydroxyglutamate according to pre-eclampsia severity*

Preeclampsia	4- hydroxyglutamate			
	No.	Mean	SD	P value
Severe	24	257.88	43.436	0.089
Mild	26	229.77	68.789	

Similarly, LDH, BUN, S. creatinine uric acid, and protein/creatinine ratio were all significantly higher in the pre-eclampsia group, whereas platelet and albumin were lower in pre-eclampsia cases compared to control.

The mean level of 4-hydroxyglutamate was significantly higher in the case group (mean ± SD = 243 ± 59 pg/ml) when compared with the control (mean ± SD = 90 ± 45 pg/ml), while the range was (29–351 pg/ml vs 4–185 pg/ml), with a p-value of < 0.0001, as shown in Table 4.

Regarding severity of preeclampsia there was no difference in level of 4 hydroxy glutamate between mild and severe preeclampsia as shown in Table 5.

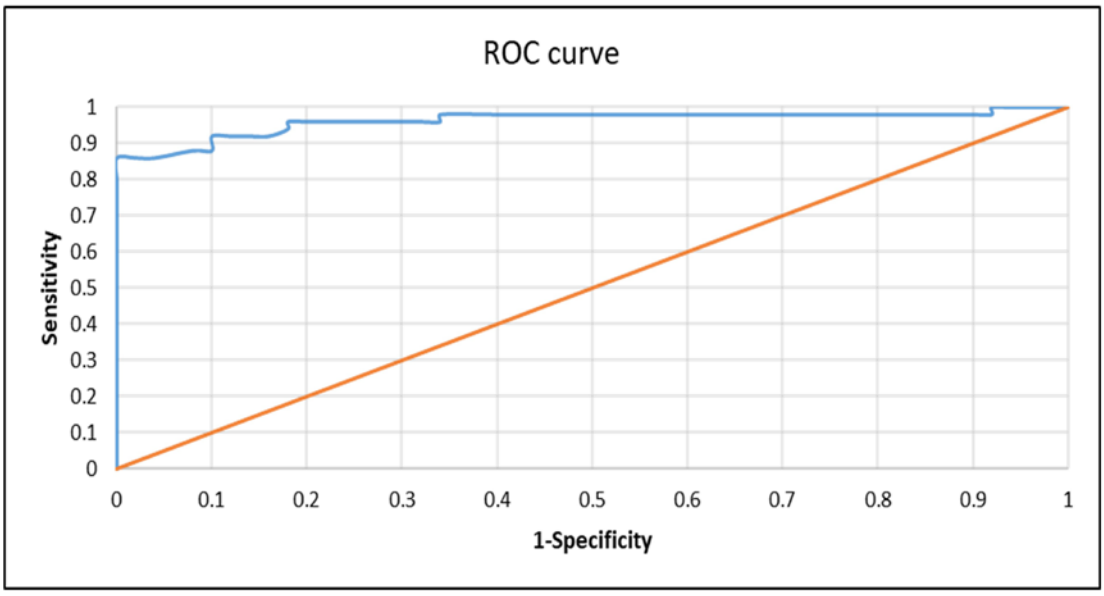

Figure 1. *ROC curve analysis*

Table 6. *Predictive ability of 4-hydroxyglutamate*

Parameter	Level
AUC	0.963
95% CI	0.922-1.000
Cutoff point (pg/ml)	≥ 142.5
Sensitivity	92%
Specificity	84%
PPV	85.2%
NPV	91.3%
Accuracy	88%
Odd ratio	5.75
95% CI	3.031-10.908

The receiver operator characteristics curve revealed that a 4-hydroxyglutamate level of ≥ 142.5 was a highly sensitive (92%) and specific (85.2%) marker of pre-eclampsia. Patients with a 4- hydroxyglutamate level of ≥ 142.5 had a 5.75-fold increased the risk of pre-eclampsia, as shown in Figure 1 and Table 6.

DISCUSSION

Treatment of hypertensive diseases during pregnancy is a distinctive challenge due to the fact that therapeutic interventions affect both the mother and the embryo simultaneously, occasionally resulting in a conflict between their well-being. Pre-eclampsia has the potential to rapidly progress to severe complications, which may lead to the death of both the mother and the infant (6).

Metabolomics is an essential element of system biology, with a primary emphasis on the analysis of fluids, including blood, urine, and excrement. It examines the small molecule metabolites present in various metabolic pathway matrices and their resulting products. In contrast to other "omics" techniques, metabolomics is a potent methodology that enables the direct evaluation of cellular/tissue biochemical activity and state by measuring metabolites and their concentrations, hence providing a pre-

cise representation of the molecular phenotype (7). Lipidomics, a specific branch of metabolic profiling (8) that has been associated with the onset and progression of a variety of diseases, including cardiovascular metabolic syndrome (9), is intricately linked to the dysregulation of lipid metabolism. Metabolomics and lipidomics have the potential to provide new and valuable information for a more comprehensive understanding of pre-eclampsia. Additionally, they may disclose the complex molecular processes that contribute to the development of pre-eclampsia.

The association of pre-eclampsia with maternal age, first pregnancy, and low socioeconomic class were reported previously (10–14), however, this was not evident in the current study probably due to the small sample size. Similarly, we did not observe an association between pre-eclampsia and previous miscarriage, whereas a meta-analysis of 68,185 patients concluded that previous miscarriage may lead to placental dysfunctional disorder causing pre-eclampsia (15). Regular antenatal care may provide a primary preventive approach for high-risk patients such as lifestyle modification and low doses of aspirin (16). This may explain the significant association between pre-eclampsia and irregular antenatal care visits in the current study which is in keeping with what has been reported by Briceño-Pérez et al. (16).

The most interesting observation reported about 4-hydroxyglutamate is that, in contrast to other protein biomarkers, like PAPP-A and PIGF, the maternal blood level of 4-hydroxyglutamate during the first trimester is significantly associated with the risk of developing pre-eclampsia, and this association is independent of maternal characteristics (17).

Collagen, whether ingested or synthesized in the body, is the primary source of 4-hydroxyproline, which is converted into 4-hydroxyglutamate in the mitochondria. Increased collagen turnover and 4-hydroxyproline release are the causes of the higher 4-hydroxyglutamate levels. Maintaining a healthy pregnancy also depends on the placenta's ability to regulate glutamate and glutamine exchange (1).

The mean level of 4-hydroxyglutamate was significantly higher in the case group than the control in the third trimester. In Sovio et al.'s study (5) which included 519 participants, they compared the level of 4-hydroxyglutamate in 194 women with pre-eclampsia with 325 normotensive women at 12, 20, 28, and 36 weeks of gestation and found that 4-hydroxyglutamate was universally elevated (from week 12 to 36) in cases of pre-eclampsia, and it was considered as a predictor for the development of pre-eclampsia when measured as early as the 12th week.

In the current study, it was determined that 4-hydroxyglutamate is a sensitive and specific marker of pre-eclampsia. AUC values of 0.963 were associated with a 5.75-fold increased risk of pre-eclampsia at the level of 142.5 pg/ml. At the 12th week of gestation, Sovio et al. determined that the AUC was 0.673 (5). However, the 4-hydroxyglutamate exhibitted no significant predictive ability for severity prediction in the current study. In their comparison of 104 cases of pre-eclampsia with 100 normotensive women, Zhao et al. (14) (n = 204) found that the sensitivity for the prediction of pre-eclampsia was 84.2%, with a specificity of 68% for mild pre-eclampsia and 75% and 86% for severe pre-eclampsia.

The elevated level of 4-hydroxyglutamate may be attributed to the effect of pre-eclampsia by the activation of gluconeogenesis with the formation of glutamine products, especially 4-hydroxyglutamate, that are normally transported across the placenta (18). The presence of inadequate oxygen supply in cells and placenta, known as a hypoxic condition, leads to a state similar to placental oxidative stress in pre-eclampsia. This is supported by the observed increase in markers of hypoxia (oxoguanine DNA glycosylase 1, hypoxia-inducible factor 1 alpha subunit) and pre-eclampsia (soluble fms-like tyrosine kinase 1) both in laboratory experiments and in living organisms (19).

In cases of pre-eclampsia, renal function tests (BUN and serum creatinine) were both elevated. This indicates that high blood pressure has a detrimental impact on the kidneys, further compounded by proteinuria, which in turn affects filtration gradients. Charles et al. (14) (n = 144) observed a comparable outcome when they compared 72 cases of pre-eclampsia and 72 normotensive women in terms of renal function and electrolytes. They discovered that deteriorating renal function was associated with an increase in the severity of pre-eclampsia. As suggested by Bellos et al. in their meta-analysis, uric acid levels are significantly elevated in pre-eclampsia cases (20). This elevation is a result of vascular injury that is induced by pre-eclampsia, which in turn activates oxidative stress and inflammatory cascades. The meta-analysis included 196 studies and constituted 39,540 women.

They discovered that serum uric was further elevated in cases of severe pre-eclampsia, eclampsia, and HELLP syndrome. The serum albumin was significantly lower in pre-eclampsia cases due to two factors: first, the urinary loss of albumin as a result of pre-eclampsia, and second, the body is under stress in the pre-eclampsia condition, which causes a decrease in albumin, a negative acute phase reactant, as a result of increased consumption, decreased production, and increased loss to the interstitial space, resulting in edema. Shi et al. (n = 618) discovered a comparable outcome when they compared 309 women with pre-eclampsia and 309 normotensive women (21). They discovered that an excessive decrease in serum albumin (from the baseline at the early third trimester) toward the end of pregnancy was associated with an increased risk of pre-eclampsia complications. In cases of pre-eclampsia, serum lactate dehydrogenase is substantially elevated. This may be attributed to a variety of factors, including tissue ischemia (placental ischemia), increased glycolysis (as a response to stress), and endothelial injury. Saleem et al. (n = 60) also discovered a comparable outcome when they compared the serum LDH levels of 30 women with pre-eclampsia and 30 normotensive women. They determined that LDH is a robust marker and predictor of pre-eclampsia (22).

CONCLUSION

The level of 4-hydroxyglutamate was increased significantly in pregnant women with pre-eclampsia in comparison to healthy women and could be used as a predicting marker with high sensitivity.

DECLARATIONS

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Dr. Noor A. Fawzi: concepts, design, literature search, clinical studies, data analysis, statistical analysis, manuscript preparation and manuscript review.

Prof. Wasan Wajdy: concepts, design, data analysis, manuscript preparation and manuscript review.

Ethics approval and consent to participate

Prior to data collection, a statement of patient by written informed consent to participate in the study as specified in the Declaration of Helsinki was sought from each patient and the information gathered was kept anonymous. Personal names were substituted with identifying numbers. The information was securely stored on a laptop protected by a password, and the data was solely used for research objectives while maintaining confidentiality.

Administrative approvals were granted from Council of Iraqi Board of Medical Specialization: registration number (EAC- 1248) on January 5, 2022. Also, the Approval of the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital: registration number (8557) was obtained on December 21, 2021.

Patient consent for publication

A statement of consent for publication was obtained from the patient according to the principles of the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools (to be included only when AI tools are used): none.

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Povezanost 4-hidroksiglutamata sa preeklampsijom

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SAŽETAK

Uvod/Cilj. Preeklampsija je jedan od glavnih uzroka perinatalnog mortaliteta. Glutamat ima ključnu ulogu u održavanju zdrave trudnoće. Stoga, cilj ove studije bio je da se utvrdi stepen povezanosti između preeklampsije i 4-hidroksiglutamatne kiseline.

Metode. Ovo je studija tipa slučaj-kontrola, sprovedena na uzorku od 100 trudnica u trećem trimestru trudnoće. Ispitivana grupa sastojala se od 26 trudnica sa blagom preeklampsijom i 24 trudnice sa teškom preeklampsijom. Kontrolnu grupu činilo je 50 normotenzivnih trudnica. Svim pacijentkinjama je određen nivo 4-hidroksiglutamata (metodom ELISA). Takođe, urađeni su testovi funkcije jetre i bubrega i analiza kompletne krvne slike i određeni nivoi mokraćne kiseline, laktat dehidrogenaze (LDH) u serumu i albumina u urinu.

Rezultati. Prosečan nivo 4-hidroksiglutamata bio je značajno viši u grupi ispitanica (srednja vrednost ± SD = 243 ± 59 pg/ml) nego u kontrolnoj grupi (srednja vrednost ± SD = 90 ± 45 pg/ml), sa opsegom 29–351 pg/ml u poređenju sa 4–185 pg/ml, i vrednošću p < 0,0001/ml. Pacijentkinje sa teškom preeklampsijom imale su više prosečne vrednosti 4-hidroksiglutamata (257,88 ± 43,436 pg/ml) nego one sa blagim oblikom preeklampsije (229,77 ± 68,789 pg/ml), premda ta razlika nije bila statistički značajna. Nivo 4-hidroksiglutamata ≥ 142,5 pokazao se kao visoko osetljiv (92%) i specifičan (85,2%) pokazatelj preeklampsije prilikom korišćenja ROC (engl. *receiver operator characteristics*) krive. Nivo 4-hidroksiglutamata ≥ 142,5 bio je povezan sa 5,75 puta većim rizikom od razvoja preeklampsije.

Zaključak. S obzirom na to da je nivo 4-hidroksiglutamata bio značajno viši kod trudnica sa preeklampsijom nego kod zdravih trudnica, može se koristiti kao prediktivni marker sa visokom osetljivosti.

Ključne reči: **preeklampsija, glutamat, laboratorijski markeri**