Homocysteine Changes in Preeclampsia

Maha Al-Bayati
CABOG

Ali Taki Al-baldawi
PhD Pathology

Abstract

Objective: To determine whether homocysteine, a relatively new risk factor for possible endothelial cell dysfunction and premature vascular disease, is elevated in pregnant women with preeclampsia.

Methods: A case-control study design conducted at Al-kadimiya teaching hospital for the period from September 2000 through April 2001. The study sample consisted of 100 pregnant women in labour subdivided into three groups (40 pregnant women with severe preeclampsia, 30 pregnant women with mild preeclampsia and 30 normotensive pregnant women as a control). Plasma homocysteine concentration measurement and observation of the maternal and fetal outcome was done for all groups.

Results: The incidence of hyperhomocysteinemia was significantly higher among patients with severe preeclampsia (80%) compared to those with mild preeclampsia (67%) and the normotensive group (7%) and the incidence of adverse maternal and neonatal outcome is significantly higher among patients with severe preeclampsia compared to the others.

Conclusion: Plasma total homocysteine concentration is elevated in pregnant women with preeclampsia during labour being significantly higher in cases with severe preeclampsia so hyperhomocysteinemia is considered a risk factor for adverse maternal and neonatal outcome.

Key words: Homocysteine, Preeclampsia, Neonatal outcome

Introduction:

Preeclampsia is considered as an acute syndrome, which is peculiar to pregnancy [1]. The presentation is very variable and although hypertension and proteinuria are the two signs most easily detected, they are not central to the pathogenesis of the disorder [2].

Maternal plasma homocysteine concentrations at various stages of pregnancy tend to be lower than in non-pregnant women [3]. This has been attributed to hemodilution and the drop in serum albumin concentration as pregnancy progresses as 70-80%of homocysteine is albumin bound [4].

There is considerable evidence that an elevated plasma homocysteine level is associated, perhaps causally, with variety of disorders in which impaired vascular function is a clinical feature. These disorders range from coronary artery disease to stroke and cognitive dysfunction [1]. In recent years several groups have proposed that elevated plasma homocysteine levels during pregnancy may be associated with impaired vascular function of the placenta, which leads to deep venous thrombosis, Abruptio placentae, preeclampsia, stillbirth, Recurrent miscarriage, and intrauterine growth restriction[1,5]. Moreover, elevated homocysteine levels have been observed in maternal plasma and amniotic fluid during neural tube defect-affected pregnancies [5].

Increased plasma homocysteine concentration has been recognized as an independent risk factor for atherosclerosis and atherothrombosis in the coronary, cerebral and peripheral vasculature [6]. The risk is proposed to include modification of endothelial function because of homocysteine exposure. The exact mechanism through which homocysteine promotes endothelial dysfunction remains unclear, but it appears to involve both cytotoxic and oxidative stress mechanisms similar to those postulated to promote endothelial dysfunction in preeclampsia. Furthermore the pathophysiology of preeclampsia shows striking similarities to that of atherosclerosis [7].

In addition, vascular endothelium in pregnant women may be more sensitive to injury: therefore, moderate elevation in homocysteine levels may lead to endothelial injury with subsequent activation of various factors that result eventually in preeclampsia [8]. Some workers found that the incidence of hyperhomocysteinemia in patients with a history of early onset preeclampsia is about seven fold higher than the incidence in the normal population [9].

This study was conducted to determine whether homocysteine, a relatively new risk factor for possible endothelial cell dysfunction and premature vascular disease, is elevated in pregnant women with preeclampsia.

Patients & Methods:

This study was conducted on 100 pregnant women presented with labour pain attending the Al-kadimiyah teaching hospital over a period of 8 months starting from September 2000 to the end of April 2001. We studied 70 preeclamptic women and 30 apparently healthy pregnant women as a control group. The criteria used for collection of cases include age range from 18-40 years, parity less than 5, gestational age range from 28-40

weeks, singleton pregnancy and no history of medical diseases.

Women included in the study were subdivided into three groups:

Group A: Forty pregnant women in labour with severe preeclampsia which was evidenced by a systolic blood pressure of ≥ 160 mmHg and diastolic blood pressure of ≥110 mmHg with proteinuria of ≥5 grams / 24hours and / or oedema.

Group B: Thirty pregnant women in labour with mild preeclampsia, which was evidenced by a systolic blood pressure of 140 mmHg and diastolic blood pressure of 90 mmHg with oedema.

Group C: Thirty apparently healthy pregnant women in labour of comparable age, parity, and stage of pregnancy, as a control group.

After medical, surgical, drug and obstetrical history was taken from all women, they were subjected to full physical and obstetrical examination. They were followed during their labour, postnatal period and puerperium with follow up of their newborn during their postnatal period.

In addition to the routine laboratory tests done, we measure the total plasma homocysteine concentration by high performance liquid chromatography (HPLC).

Neonatal outcome was assessed by estimation of Apgar score at one and 5 minutes, gestational age at birth, birth weight, intrauterine growth restriction, respiratory distress syndrome, days of admission to the neonatal care unit and neonatal death.

Statistical analysis of the data was performed using the following tests:

1- Analysis of variance (AOV) and the f-test of significance.
2- 95% confidence interval multiple comparisons test.
3- Chi-square test.
4- t-test.

Results:

After collection and categorization of data from 100 women included in the study and control groups, statistical analysis revealed that there was no significant differences among the three groups in age and parity.

Table1 shows the incidence of hyperhomocysteinemia for all groups, a higher percentage among group A (80%) compared to B (67%) and group C (7%).

Table 2 show a high significant difference in the mean plasma total homocysteine concentration (P-tHcy conc.) among the three compared groups, being higher in-group A than in group B and C and that of group B higher than in-group C.

Table 1: Incidence of hyperhomocysteinemia for all groups

	A	**B**	**C**
P-t Hcy conc.(µmol/L)	No. (%)	No. (%)	No. (%)
Normal (5-15)	8 (20)	10 (33)	28 (93)
Increased (15.6-21.1)	32 (80)	20 (67)	2 (7)
Total	40 (100)	30 (100)	30 (100)

(P-t Hcy Conc. = Plasma total Homocysteine Concentration)

Table 2: Mean P-tHcy Conc. For all groups

Mean P-tHcy Conc. µmol/l ± SE		
A	**B**	**C**
21.1± 8.988	15.6 ± 7.233	9.5 ± 4.71

(SD = standard deviation)

The incidence of eclampsia and imminent eclampsia were significantly higher in-group A (6 and 7%) respectively with no such complications noted in-group B and C. A significant difference in the incidence of preterm labour was found among the three compared groups being higher in-group A (17%) than in-group B (9%) and C (3%). No significant difference found in the incidence of placental abruption among the three compared groups. Regarding the mode of delivery, there was no significant difference in group A (spontaneous vaginal delivery 19% and caesarean section 21%) while in group B and C the incidence of spontaneous vaginal delivery (20 and 21% respectively)was higher than the incidence of caesarean section (10 and 9% respectively).

The maternal outcome in hyperhomocysteinemic patients for group A and B is summarized in table 3. The incidence of eclampsia and imminent eclampsia was significantly higher in-group A than in-group B ($P<0.05$) but no significant difference in the incidence of preterm labour and placental abruption was found between the two groups ($P>0.05$). Regarding the mode of delivery, there was no significant difference for patients in-group A ($P>0.05$) but there was a significant difference in-group B ($P<0.001$). The incidence of spontaneous vaginal delivery was higher than that of caesarean section. The mean P-tHcy conc. was noted to be significantly higher in-group A than group B ($P<0.000001$). Regarding the mean hospitalization days, there was a significant difference between the two groups ($P<0.00001$) being more in-group A.

Table 3: Maternal outcome in hyperhomocysteinemic patients for group A and B

FINDING	A (No. 32)	B (No. 20)
Eclampsia	6 (18%)	0 (0%)
Imminent eclampsia	7 (22%)	0 (0%)
Preterm labour	15 (47%)	6 (30%)
Placental abruption	4 (13%)	1 (3%)
SVD	14 (44%)	15 (75%)
Caesarean section	18 (56%)	5 (25%)
Mean P-tHcy Conc.± SD	23.5 ± 5.260	18.50 ± 2.862
Mean hosp. days ± SD	8.27 ± 3.84	2.30 ± 2.146

SVD (spontaneous vaginal delivery). Hosp. (hospitalization).

The neonatal outcome for the three compared groups revealed that the incidence of prematurity was significantly higher in group A (53%) than in-group B and C (20 and 7% respectively), $P<0.0001$. There was a significant difference in the incidence of intrauterine growth restriction between the three groups, being higher in-group A (7%, 2%, 0%) respectively with a P Value of <0.05. No significant difference was noted among the three groups in the incidence of respiratory distress syndrome, perinatal death, and intrauterine death with a P value of >0.05, though more incidence in-group A in comparison to the other two groups.

Regarding the mean gestational age (week) at birth there was a significant difference between the three compared groups ($P<0.001$), being lower in group A (35.70±0.45) and B (36.30±0.56) than that in-group C (38.03±0.37). A significant difference was noted between the three groups in the mean birth weight (g); it was significantly lower in group A (2510±0.16) and B (2670±0.16) than in-group C (3280±0.10). Regarding the Apgar score at 1 and 5 minutes there was a significant difference between the three groups ($P<0.0001$), it was significantly lower for group A and B than in group C ($P<0.05$). The mean days of hospitalization in the neonatal care unit was significantly higher in-group A (3.28±0.18) than in group B (1.35±0.19) and group C (0.96±0.17) with a P value <0.001.

Table 4 summarizes the neonatal outcome in hyperhomocysteinemic patients of group A and B.

It shows a significant difference in the incidence of prematurity between the two groups being more in-group A. No significant difference in the incidence of intrauterine growth restriction (IUGR), respiratory distress syndrome (RDS), perinatal death (PND), and intrauterine death (IUD), between the two groups ($P>0.05$) though the incidence being more in group A.

The mean gestational age (GA) at birth for group A was lower than that for group B but the difference was not significant (P>0.05). No significant difference in the mean birth weight (BW) between the two groups (P>0.05) though being lower in-group A than in-group B.

Regarding the Apgar Score (A/S) at 1 minute, there was a significant difference between the two groups (P<0.05) being lower in group A, but no significant difference in the A/S at 5 minutes between the two groups (P>0.05). The mean days of hospitalization in the neonatal care unit (NCU) was higher in-group A than in-group B but the difference was not significant (P>0.05).

Table 4: Neonatal outcome in hyperhomocysteinemic patients for group A and B

FINDING	A (No. 32)	B (No. 20)
Prematurity	19 (59%)	5 (25%)
IUGR	6 (19%)	2 (10%)
RDS	6 (19%)	1 (5%)
PND	4 (13%)	1 (5%)
IUD	4 (13%)	1 (5%)
Mean GA (week) ± SD	35.48 ± 2.771	36.05 ± 3.309
Mean BW (g) ± SD	2380 ± 0.904	2590 ± 0.894
Mean A/S at 1 minute ± SD	4.32 ± 1.866	5.62 ± 1.878
Mean A/S at 5 minutes ±SD	6.74 ± 2.828	7.64 ± 2.683
Mean NCU days ± SD	3.70 ± 2.205	2.56 ± 1.073

Discussion:

The present study showed that plasma total homocysteine concentration in preeclamptic women presented with labour pain were significantly higher than those of normotensive women. This result is consistent with that of Aleksandar Rajkovic who found that

Plasma homocysteine levels were significantly higher among women with preeclampsia than among women without it [8]. He explained this result upon the fact that the vascular endothelium in pregnancy is more sensitive to injury and moderate elevation in homocysteine levels may lead to endothelial injury with subsequent activation of various factors that result in preeclampsia. Robert Powers concluded that the concentration of plasma total homocysteine was higher in women with preeclampsia than in healthy pregnant women [10]. He proposed that there is a modification of endothelial function because of homocysteine exposure.

The exact mechanism through which homocysteine promotes endothelial dysfunction appears to involve both cytotoxic and oxidative stress mechanisms similar to those postulated to promote endothelial dysfunction in preeclampsia(11) and this may be due to the fact that homocysteine is one of the most important causative factors for endothelial dysfunction and premature vascular disease in preeclampsia. Also this study showed a strong association between the elevated plasma homocysteine levels and the severity of preeclampsia as reflected by the high levels of mean plasma total homocysteine concentration among patients in group A (21.1±1.42) µmol/L compared to (15.6±1.32) µmol/L among patients in group B and (9.5±0.86) µmol/L in group C. The incidence of hyperhomocysteinemia among patients with severe preeclampsia was (80%) compared to those with mild preeclampsia (67%) and control group (70%). These findings were in agreement with that of Dekker et al. who found an increased plasma homocysteine levels in a subset of women with early onset preeclampsia(9). This means that plasma homocysteine levels are related to the severity of preeclampsia. Regarding the maternal outcome, our study revealed that in hyperhomocysteinemic patients with severe preeclampsia there was a high incidence of eclampsia (18%), imminent eclampsia (22%), placental abruption (13%) and preterm labour

(47%) while in mild preeclamptic patients the only significant complication was preterm labour (30%).

The exact cause of eclamptic fit is unknown. In a study done by Kim Koh in 1987 on rats concluded that homocysteine is metabolized to excitatory amino acid neurotransmitters, such as homocysteic acid and cystiene sulfinic acid, which can cause seizures and excitotoxic neuronal death in rats [12], so elevated homocysteine levels in susceptible pregnant women might contribute to eclamptic convulsions. Rajkovic et al. in a case control study found that immediately postpartum, homocysteine concentrations in eclamptic and preeclamptic African women were significantly higher than those of normotensive women [13].

Goddijn-Wessel in his study found that hyperhomocysteinemia is associated with increased incidence of placental abruption and infarction [14]. Recently, Steegers-Theunissen et al. [15] and Wouters et al. [5] have demonstrated that mild hyperhomocysteinemia is associated with embryotoxicity (leading to neural tube defects or spontaneous abortion) and/or vascular toxicity (leading to placental infarcts or abruption). This might explain the high incidence of placental abruption in women presented with preeclampsia.

Regarding the neonatal outcome, the high incidence of prematurity in-group A may be due to termination of pregnancy because of maternal indication and complication of preeclampsia or due to fetal causes such as severe intrauterine growth restriction and fetal distress. On the other hand, prematurity in the other two groups was mainly due to spontaneous preterm labour and preterm premature rupture of membranes. These results are in agreement with that of Rajkovic et al. who found women with preeclampsia delivered significantly earlier (35±4 weeks) than controls (40±1 week)(8).

Recent literatures revealed that hyperhomocysteinemia is proposed to alter endothelial functions; therefore Tayler in his study found a striking correlation between homocysteine concentration and that of cellular fibronectin in preeclampsia [16] which suggests that homocysteine may have a graded effect on endothelial cell function and cellular fibronectin release. Hyperhomocysteinemia may be due to genetic defects or nutritional defects involving inadequate intake of folic acid and vitamin B12. Folic acid significantly reduces plasma homocysteine level during pregnancy and is currently recommended for all women as it may reduce the risk of obstetric complications related to high levels of homocysteine including preeclampsia, spontaneous abortion and placental abruption[4]. Finally oestrogen and cortisol treatment have been reported to decrease homocysteine concentration in male rats[17], so the increment in these hormones during pregnancy may be one of the mechanisms that mediate the specific decrease in homocysteine and may be used in the future as a treatment for hyperhomocysteinemia.

Conclusion:

From this study, we conclude that plasma total homocysteine concentration is elevated in pregnant women with preeclampsia during labour and there is a strong association between plasma total homocysteine concentration and the severity of preeclampsia. The increased plasma homocysteine levels are associated with adverse maternal and neonatal outcome thus homocysteine can be used as a screening marker for early development of preeclampsia

References:

1-Charles R. Brinman III. Hypertensive disorders of pregnancy. Essentials of obstetrics and gynaecology, 2nd edition, W.B. Saunders Company, Philadelphia, 1992; 163-74.

2-S.C.Robson. Hypertensive disorders of pregnancy. Dewhurst's textbook of obstetrics and gynaecology for postgraduates, 5th edition, Blackwell Science, London, 1995; 175-215.

3-Anderson A, Hultberg B, Brattstrom L, Isaksson A. Decreased serum homocysteine in pregnancy. Clin Chem. 1992; 30:377-9.

4-Mark C. Walker, MD, Graeme N. Smith, MD, PhD, Sherry L. Perkins, PhD, Erin J. Keely, MD and Peter R. Garner MD, Msc. Changes in homocysteine levels during normal pregnancy. Am J Obstet Gynaecol. 1999; 180:660-64.

5-Wouters MGAJ, Boers GHJ, Blom HJ. Hyperhomocysteinemia: a risk factor in women with unexplained recurrent early pregnancy loss. Fertil Steril 1993; 60:820-5.

6-Mccully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. Am J Pathol 1969; 56:111-28.

7-Roberts JM, Taylor RN, Goldfein A. Clinical and biochemical evidence of endothelial dysfunction in the pregnancy syndrome preeclampsia. Am J Hypertens 1991; 4:700-8.

8-Aleksandar Rajkovic, PhD, MD, Patrick M. Catalano, MD, and M. Rene Malinow MD. Elevated homocysteine levels with preeclampsia. Br J Obstet Gynaecol 1997; 90:168-71.

9- G. A. Dekker, MD, PhD, J.I.P. de Vries, MD,PhD, P.M. Doelitzsch, MS, P.C. et al. Underlying disorders associated with severe early onset preeclampsia. Am J Obstet Gynaecol. 1995; 173:1042-8.

10- Robert W. Powers, PhD, Robert W. Evans, PhD, Alana K. Majors, PhD. Plasma homocysteine concentration is increased in preeclampsia and is associated with evidence of endothelial activation, Am J Obstet Gynaecol; 1998; 179:1605-11.

11- Mayer EL, Jacobsem DW, Robinson K. Homocysteine and coronary atherosclerosis. J Am coll cardiol 1996; 517-27.
12- Kim J, Koh Jy, Choi D.L. Homocyteate is a potent neurotoxin on cultured cortical neurons. Brain Res 1987; 437:103-6.
13- Aleksandar Rajkovic, PhD, MD, Kassam Mahomed, MRCOG, MD, M. Rene Malinow, MD. Plasma homocysteine concentrations in eclamptic and preeclamptic African women Postpartum. Br J Obstet Gynaecol 1999; 94:355-60.
14- Goddijn-wessel TA, Wooters MC, Vande Molen EF, et al. Hyperhomocysteinemia: a risk factor for placental abruption or infarction. Eur J Obstet Gynaecol Reprod Biol 1996; 66:239.
15- Steegers-Theuissen RPM, Boer GHJ, Trijbels et al. Maternal Hyperhomocysteinemia: A risk factor for neural tube defects. Metabolism 1994-43:1475-80.
16- Tylor RN, Crumbleholme WR, Friedman SA, Jones LA. High plasma cellular fibronectin levels correlate with biochemical and clinical features of preeclampsia but cannot be Attributed to hypertension alone. Am J Obstet Gynaecol 1991; 165:895-901.
17- Tait JF. The use of isotopic steroids for the measurement of production rates in vivo. J Clin Endocrinol Metab 1998; 24:1285-97.

إنزيم الكرياتين والقياس الوحيد لهرمون البروجستيرون في مصل الدم الامومي للتكهن بالحمل المنتبذ

هدف الدراسة: تقدير دور قياس انزيم الكرياتين والقياس الوحيد لهرمون البروجستيرون في مصل الدم الامومي في التكهن عن الحمل المنتبذ.

اجريت هذة الدراسة في مستشفى الكاظمية التعليمي / قسم النسائية والتوليد للفترة من آذار 2001 إلى نيسان 2002.

شملت الدراسة 60 سيدة و قسمت السيدات الى ثلاثة مجاميع :

1. المجموعة ا : تتالف من 20 سيدة تعاني من الحمل المنتبذ مثبتة عن طريق الجراحة والفحص االنسيجي .
2. المجموعة ب: تتألف من 20 سيدة تعاني من اسقاط منسي أو إسقاط تلقائي وفترة حمل قابلة للمقارنة .
3. المجموعة ج: تتالف من 20 سيدة حامل تتمتع بصحة جيدة وفترة حمل قابلة للمقارنة.

شملت الدراسة الفحوصات المختبرية التالية:

1. قياس مستوى انزيم الكرياتين في مصل الدم لجميع المجاميع.
2. قياس مستوى هرمون البروجستيرون في مصل الدم لجميع المجاميع.
3. الفحص النسيجي لبيان عمق انغراس الارومة الغازية للطبقة العضلية من انبوب فالوب للمجموعة ا .

تمخض تحليل النتائج احصائيا عن مايلي :

1. معدل مستوى انزيم الكرياتين في مصل الدم اعلى لدى السيدات في المجموعة ا عنه في المجموعتين ب وج.
2. معدل مستوى هرمون البروجستيرون في مصل الدم أدنى لدى السيدات في المجموعتين ا وب عنه في المجموعة ج.
3. معدل مستوى انزيم الكرياتين في مصل الدم اعلى في حالة الحمل المنتبذ المتمزق عنه في حالة الحمل المنتبذ الغير متمزق.
4. معدل مستوى هرمون البروجستيرون اعلى في حالة الحمل المنتبذ المتمزق عنه في حالة الحمل المنتبذ الغير متمزق .
5. وجدت علاقة ايجابية وثيقة بين مستوى انزيم الكرياتين وهرمون البروجستيرون في مصل الدم في المجموعة ا .

تم استنتاج مايلي :

1) الارتفاع في مستوى انزيم الكرياتين في مصل الدم المصاحب للتلف العضلي لانبوب فالوب يسبق تمزق الانبوب ويمكن الاستعانة بة في التمييز بين الحمل ألمنتبذ المتمزق والغير المتمزق.

2) القياس المزدوج لإنزيم الكرياتين وهرمون البروجستيرون في مصل الدم في حالة الحمل المنتبذ المشكوك يمتلك صحة كشفية اعلى من القياس المنفرد لاي منهما .