Liver Function Tests as Probable Markers of Preeclampsia - A Prospective Study Conducted in Riyadh

Preeklampsi Muhtemel Belirteçleri olarak Karaciğer Fonksiyon Testleri - Riyad, Suudi Arabistan'da Yapılan Bir Prospektif Çalışma

Preeklampsi Belirteci olarak Karaciğer Fonksiyon Testleri / Liver Function Tests as Marker of Preeclampsia

Noura Al-Jameil[1], Hajera Tabassum[1], Huda Al-Mayouf[2], Amal Ali Al-Shenefy[2], Farah Aziz Khan[1]
[1]Department of Clinical Laboratory Sciences, King Saud University, Riyadh, Saudi Arabia.
[2]Department of Obstetrics and Gynecology, King Saud Medical City, Riyadh, Saudi Arabia.
[3]Faculty of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.

The authors are grateful to Research Center of the "Center for Female Scientific and Medical Colleges", Deanship of Scientific Research, King Saud University for funding the research

Özet

Amaç: Preeklampsi gelişimi yüksek tansiyon ve proteinüri ile karakterizedir. Tüm gebeliklerin % 5 etkiler ve maternal ve fetal morbidite ve mortalite için büyük bir katkıda bulunuyor. İşte iyi bir tahmin preeklampsi ve ilişkili hepatik disfonksiyon için tüm ölçütleri karşılayan tek bir test yok. Çalışmanın bu nedenle karaciğer enzimleri rolünün değerlendirilmesinde preeklampsi marker olarak değerlendirmek için yürütülen. Gereç ve Yöntem: 120 gebe oluşan çalışma üç gruba ayrılır: normal hamile kadınlar, preeklampsi riski yüksek olan ve preeklampsi ile kadınlar. AST, ALT, ALP ve karaciğer serum düzeyleri analiz edildi ve klinik özellikleri karşılaştırma ve biyokimyasal parametrelerin kontrolü olan olguların t-testi ile tek yönlü ANOVA izledi tarafından gerçekleştirildi. Bulgular: Önemli artış vardı ($P < .001$) serum düzeyleri artmış ALT ve ALP preeklampsi grubundaki göre kontrol etmek ve yüksek risk ve evde beslenen preeklampsi grubu. AST Düzeyleri arasında da anlamlı ($P < .05$) ne zaman preeklamptik grubun karşılaştırıldığında kontrolü ve yüksek risk grubu. Tartışma: Bu artış, karaciğer enzimleri yüksek risk grubu ve evde beslenen preeklampsi grubu hepatik disfonksiyon veya anormal karaciğer işleyişi sonuçlandı ve gebeliğin erken dönemlerinde predictor preeklampsi tanısında olarak hareket olabilir çalışma sonucuna varılıyor.

Anahtar Kelimeler

Karaciğer Enzimleri; Hipertansiyon; Hepatik Disfonksiyon; Preeklampsi

Abstract

Aim: Preeclampsia is characterized by development of high blood pressure and proteinuria. It affects 5–8% of all pregnancies and is a major contributor to maternal and fetal morbidity and mortality. There is no single test that fulfills all the criteria for a good predictor of preeclampsia and associated hepatic dysfunction. The present study was therefore undertaken to assess the role of liver enzymes as marker in prediction of preeclampsia. Material and Method: The study comprised of 120 pregnant women divided into three groups: normal pregnant women, women with high risk of preeclampsia and women with preeclampsia. Serum levels of AST, ALT, ALP and LDH were analyzed and comparison of clinical characteristics and biochemical parameters of cases with control was performed by t-test followed by one way ANOVA. Results: There was significant increase ($P < .001$) in the levels of serum ALT and ALP in preeclampsia group compared to control and between high risk and PET group. Levels of AST also increased significantly ($P < .05$) when preeclamptic group was compared with control and high risk group. Discussion: The study concludes that increase in liver enzymes in high risk group and PET group resulted due to hepatic dysfunction or abnormal liver functioning and may acts as predictor in diagnosis of preeclampsia in early stages of pregnancy.

Keywords

Liver Enzymes; Hypertension; Hepatic Dysfunction; Preeclampsia

DOI: 10.4328/JCAM.2200 Received: 29.11.2013 Accepted: 07.12.2013 Published Online: 01.07.2015 J Clin Anal Med 2015;6(4):497-500
Corresponding Author: Noura Al Jameil, Department of clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh.
T.: +966 555269279 E-Mail: noura_jameil@yahoo.com

Introduction

Preeclampsia is a multisystem and multifactorial disease that affects both mother and the fetus by vascular dysfunction and by intrauterine growth restriction.[1] It is characterized by development of high blood pressure (hypertension) and proteinuria after 20 weeks of gestation and affects about 5-8% of all pregnancies. Several complications have been reported with this disease and it remains a major cause of maternal and fetal morbidity and mortality worldwide.[2] In preeclampsia the systolic BP is 140 mmHg and diastolic BP 90 mmHg in a woman with previously normal blood pressure and with proteinuria about 0.3 gm in a 24-hour urine collection. Severe preeclampsia is associated with one or more of elevated blood pressure 160 mmHg systolic, or 110 mmHg diastolic, on two occasions at least 6 hours apart with proteinuria >5 g in a 24-hour urine collection. The other functional symptoms are headache, hyper reflexia, oliguria, epigastric or right upper quadrant pain, impaired liver function, and thrombocytopenia (HELLP syndrome).[3] The main cause of preeclampsia is vasoconstriction and thickening of vascular media which decreases vascular capacity and increases peripheral resistance. The precise etiology of preeclampsia is not still clearly known. It affects almost every organ like kidney, CNS, haematological system, and the liver.

Risk factors for preeclampsia include extremes of maternal age (<16 years and >45 years), primiparity, gestational diabetes, obesity, renal disease, pre-existing hypertension, family history, and occurrences in a previous pregnancy.[4]

During pregnancy, the serum estrogen and progesterone levels increase progressively and affect metabolic, synthetic and excretory hepatic functions.[5] Changes in liver function test values during pregnancy may be physiological but may also present as an initial sign of pathological conditions. Normal pregnancy is generally associated with a mild increase in serum alkaline phosphatase (ALP) but with normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations. In contrast to normal pregnancy, in preeclampsia AST and ALT concentrations were found to increase.[6] Liver dysfunction during preeclampsia has serious consequences. Several standard biochemical and hematological parameters such as liver enzymes, was found to have a significant prognostic value in the prediction of preeclampsia.[7]

The present study was undertaken in view that abnormal liver function tests occur in 20% to 30% pregnancies complicated by preeclampsia and is associated with poor maternal and fetal outcome. As there is growing number of cases of preeclampsia in women of Saudi Arabia, we aimed to evaluate liver markers that are generally available and can be easily used in everyday practice for the prediction of preeclampsia. The levels of AST, ALT, LDH, ALP and bilirubin as markers for the prediction of preeclampsia were evaluated, which could be further useful in diagnosis of preeclampsia.

Material and Method

Study Population: The study was conducted in the Department of Clinical laboratory Sciences, King Saud University and Section of Obstetrics and Gynecology, King Saud Medical City Hospital, Riyadh from September 2012 to October 2013. The study was approved by hospital's ethics committee. Informed consent was obtained from patients before blood sampling.

The study consisted of 120 pregnant women divided into three groups- control group (40) which included healthy normotensive pregnant women, women at high risk of preeclampsia (HR group-40) and remaining 40 diagnosed with preeclampsia (PET group), attending antenatal OPD or labor room in their third trimester of pregnancy. Women in high risk group were included based on the following criteria: pregnant women with body mass index (BMI) of 35 or more, with mild hypertension or those with preeclampsia, gestational diabetes, IUGR (intrauterine growth restriction) or pre-term delivery in previous pregnancies and those with family history of preeclampsia. Selection of preeclamptic group and the diagnosis was based on the definition of American College of Obstetrics and Gynecologists.[3]

On admission, venous serum samples were collected when the patients were in the supine position prior to commencement of intravenous therapy. At the time of blood collection, urine protein was measured by dipstick and was graded on a scale of 0-4+ (0,none; 1+,30 mg/dl; 2+,100 mg/dl; 3+,300-1,999 mg/dl; 4+,at least 2,000 mg/dl). Blood samples obtained from patients attending OPD or admitted into hospital, were analyzed for complete blood count, measurement of serum albumin, bilirubin and activity of liver specific enzymes like AST, ALT and ALP.

Serum levels of AST, ALT, ALP, LDH, bilirubin and albumin were determined in the biochemical analyzer, COBAS INTEGRA Autoanalyser 800. Serum AST, ALT and ALP was measured using IFCC liquid ver.,2. Total bilirubin was estimated in the same autoanalyser using diazo reagent and albumin was determined using bromocresol green dye. Hematocrit (Hct) concentration was measured in automated Cell Dyne 3700 analyser and platelet count was obtained using automatic reader, STA compact, Mediserv, UK.

Statistical analysis

The results were expressed as Mean ± S.D. Statistical analyses were performed using SPSS software. Comparison of clinical characteristics and biochemical parameters of cases with control among the groups was performed by t-test followed by one way ANOVA.

Results

The mean and standard deviation values of the clinical characteristics of the control and cases are shown in 'Table 1'and '2'. Age and hematocrit among control, HR group and PET group were not significantly different. Preeclamptic group has high gestational age compared to control and HR group. BMI of HR group (37.36 ± 9.005 kg/m2) was found to be significantly high compared to control and PET group (29.94 ± 6.05 and 35.12 ± 6.06 kg/m2 respectively). The comparison of biochemical parameters within the three groups are represented in 'Table 3'. There was no significant difference in BMI between control and PET group.

The mean value of systolic arterial blood pressure (sATP) of control group and HR group was 113.56 ± 13.93 mmHg and 124.70 ± 16.21mmHg respectively, while in PET group the sATP was 167.00 ± 24.43 mmHg. There was significant difference in the value of sATP ($P < .05$) among control and HR group, and $P < .001$ was observed between control and PET group and between

Table 1. Mean and standard deviation values of the clinical characteristics in control and cases

	Control group (n=40)	High risk (HR) group (n=40)	Preeclamptic group (n=40)
Age(years)	31.20 ± 5.84	34.26 ± 6.69	31.55 ±6.14
BMI(kg/m2)	29.94 ± 6.05	37.36 ± 9.00	35.12 ±6.06
Gestational age(weeks)	31.17±5.33	30.55±6.33	33.72±3.70
Hematocrit (%)	34.75 ±4.30	34.48 ±3.55	32.76 ±3.71
Platelet count(10^3/µl)	266.17 ±84.83	209.82 ±47.64	156.65 ±52.21
sATP(mmHg)	113.56 ±13.93	124.7 ±16.21	167. 0 ±24.43
dATP(mmHg)	67.66 ±9.38	74.45 ±19.14	98.51 ±11.16

Each value represents mean ± SD

Table 2. Mean and standard deviation values of the markers of liver function test in control and cases

	Control Group (n=40)	High risk (HR) group (n=40)	Preeclamptic group (n=40)
Serum Albumin (g/l)	33.10 ±8.90	27.53±4.76	22.07 ±3.31
Serum Total bilirubin (µmol/L)	31.71±5.33	30.35±6.33	33.72±3.70
AST (U/L)	17.07±7.24	25.51±9.78	46.89±13.60
ALT (U/L)	36.70 ±5.12	58.70±15.42	95.95±21.0
ALP (U/L)	158.55±89.05	149.61±43.22	284.6±146.0
LDH(U/L)	201.27 ±50.73	252.27 ±57.43	360.95 ±78.68

Table 3. Comparison of the clinical characteristics between control and cases

	Control with high risk group		High risk group with Preeclampsia		Control group with Preeclampsia	
	t	p	t	p	t	p
BMI (kg/m2)	4.626	<0.001*	3.23	0.003**	1.395	0.16
Gestational age (weeks)	0.698	0.48	2.85	<0.05**	2.15	0.06
Hematocrit (%)	0.31	0.75	1.98	0.096	2.30	0.06
Platelet count (10^3/µl)	3.964	<0.001*	3.741	<0.001*	7.705	<0.001*
sATP (mmHg)	2.63	0.01**	10.07	<0.001*	12.64	<0.001*
dATP (mmHg)	2.16	0.033**	7.66	<0.001*	9.762	<0.001*
Serum Albumin (g/l)	4.04	<0.001*	3.94	<0.001*	7.96	<0.001*
AST (U/L)	3.57	<0.001*	9.06	<0.001*	12.64	<0.001*
ALT (U/L)	6.41	<0.01**	10.85	<0.001*	17.27	<0.001*
ALP (U/L)	0.39	0.69	5.92	<0.001*	5.53	<0.001*
LDH (U/L)	3.59	<0.001*	7.66	<0.001*	11.26	<0.001*
Bilirubin (µmol/L)	0.69	0.48	2.85	0.01**	2.15	0.06

*P < .001 and **P < .05

HR with PET group. The diastolic arterial blood pressure (dATP) was found to be high in PET group (98.51 ± 11.16) compared to control and HR group (67.66 ± 9.38 and 74.45 ± 19.14 respectively). We observed a significant difference in dATP between control and PET, HR and PET group (P < .001) and significant difference between control and HR group (P < .05). In contrast to this, platelet count was found to decrease significantly (p<0.001) in PET group compared to control and HR group.

Mean and standard deviation values of the markers of liver function test in control, high risk (HR) and preeclampsia group (PET) are given in Table 2. The mean value of AST activity in PET group (46.89± 13.60 U/L) was significantly higher (p<0.05) than HR and control group (25.51 ± 9.78 and 17.07 ± 7.24 respectively). There was significant difference (p<0.001) when PET was compared with HR and control group. Parallel to AST, the mean value of ALT activity in PET group (95.95±21.01 U/L) was significantly higher than HR and control group (58.7±15.4 and 36.7 ±5.12 respectively). There was significant difference (p<0.001) when levels of ALT were compared among all the groups, and p<0.01 was observed between control and PET group.

Similarly, activity of ALP was found to increase significantly (p<0.001) in PET group (284.6±146.0) compared to control and HR group (158.5±89.0 and 149.6±43.2 respectively).There was significant difference in ALP levels (p<0.001) in PET group compared to HR group and control. However, there was no significant difference in levels of ALP between HR group and control. The mean value of LDH was found to be high in PET group compared to control and HR group. There was significant difference in LDH value among all the groups (P < .001). On the other hand, there was slight increase in total bilirubin in PET group compared to control group. However, this increase in levels of total bilirubin was not statistically significant.

In contrast to serum ALT, AST and ALP, serum albumin was found to decrease significantly in PET group compared to control and HR group. The decrease in serum albumin levels was significantly different (P < .001) among all the groups studied.

Discussion

There are numerous pathophysiological abnormalities of preeclampsia. Some of the reported abnormalities include placental ischemia, generalized vasospasm, abnormal hemostasis with activation of the coagulation system, vascular endothelial dysfunction, abnormal nitric oxide and lipid metabolism, leukocyte activation, and changes in various cytokines as well as insulin resistance. It is possible that these pathophysiological abnormalities may also influence the liver and cause partially elevated liver enzymes, even before the appearance of preeclampsia. Possibly, these changes occur in large extent and are translated into a full clinical presentation of preeclampsia, during late pregnancy.

Abnormalities in liver function tests (LFTs) includes the elevation in levels of static biochemical tests like AST, ALT, alkaline phosphatase, bilirubin, and albumin. Cellular injury in the liver causes release of AST and ALT. ALT is a more specific indication of liver disease, whereas AST elevations may be secondary to damage of other organs (heart, kidney, brain, intestine and placenta). Alkaline phosphatase is associated with cellular membranes, and its elevated levels are caused by injury to the liver, bone, kidneys, intestines, placenta, or leukocytes. In the liver, the enzyme is located in the bile canaliculi. Biliary obstruction induces increased synthesis of alkaline phosphatase and spillage into the circulation.

The present study examined the role of liver enzymes as marker in prediction of preeclampsia. Increased serum enzyme concentrations are conventionally interpreted as a marker of alcohol abuse and/or liver damage. We therefore included subjects who were free of evidence of hepatitis B or C virus infection, non alcoholics or active liver damage.

In preeclampsia elevated levels of liver function tests are observed. ALT and AST levels are elevated, and hyper-bilirubinemia

occurs, especially in the presence of haemolysis. The lesion due to periportal hemorrhagic necrosis in the periphery of the liver lobule probably causes elevation in the levels of liver enzymes in serum.[8] These conditions have been associated with insulin resistance (particularly hepatic), higher blood pressure, obesity, central fat distribution, glucose intolerance, dyslipidemia that results in preeclampsia. In the present study we observed an increase in levels of AST and ALT in preeclamptic group compared to normotensive control women. Our results are in agreement to that of Knapen et al., and Elad Mei-Dan et al..[9-11]

Low platelet count and abnormal liver function tests observed in our study are in consistent with previous reports.[12] Similar to our findings, Makuyana et al., also observed increase in AST and ALP levels in preeclamptic group compared to normotensive pregnant women. Whereas non-significant difference in levels of bilirubin, ALT and serum albumin in preeclamptic group and normotensive pregnant women was observed in their study.[13] On contrary, significant difference in levels of ALT and serum albumin were observed in the present study.

Conclusion

Based on the results obtained in our study we conclude that liver function tests particularly AST, ALT and ALP levels can be used as a potential biomarker for predicting preeclampsia. The abnormal increase in the levels of liver enzymes in high risk group compared with normal pregnant women suggests that liver dysfunction along with hypertension in early stages of pregnancy can lead to preeclampsia.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

The authors are grateful to Research Center of the "Center for Female Scientific and Medical Colleges", Deanship of Scientific Research, King Saud University for the grant and King Saud Medical City Hospital, Riyadh, K.S.A for providing samples and facilities for completion of the study.

References

1. Noura A.J, Tabassum H, Farah A.K, Ansar S, Ali M.N. Relationship between dietary factors and risk of Preeclampsia: A Systematic review. South Asian J Exp Biol 2013; 3(1): 01-09

2. Thangaratinam S, Ismail K.M, Sharp S, Coomarasamy A, Khan K.S. Tests in prediction of pre-eclampsia severity review group. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 2006; 113: 369-78.

3. ACOG Committee on Obstetric Practice. ACOG practice bulletin.Diagnosis and management of preeclampsia and eclampsia. Obstet Gynecol 2002; 99(1) :159–67.

4. Walsh S.W, Vaughan J.E, Wang Y, Roberts L.J. Placental isoprostane is signifi cantly increased in preeclampsia. FASEB J 2000; 14:1289–96.

5. Bacq Y, Zarka O, Bréchot J.F, Mariotte N, Vol S, Tichet J, Weill J. Liver function tests in normal pregnancy: a prospective studyof 103 pregnant women and 103 matched controls. Hepatology 1996; 23:1030–1034.

6. He S, Bremme K, Kallner A, Blomback M. Increased concentrations of lactate dehydrogenase in pregnancy with preeclampsia: a predictor for the birth of small-for-gestational-age infants. Gynecol Obstet Invest 1995; 39, 234–238.

7. Delic R, Stefanovic M. Optimal laboratory panel for predicting preeclampsia. J Matern Fetal Neonatal Med 2010; 23:96–102.

8. Simith L.R.Jr, Moise K.H.Jr, Dildy G.A, Carpenter R.J.Spontaneous rupture of liver during pregnancy: current therapy.Obstet Gynecol 1991;77:171–5

9. Knapen M.F, Mulder T.P, Bisseling J.G, Penders R.H, Peters W.H, Steegers E.A. Plasma glutathione-s-Transferase Alpha-1-1. A more sensitive marker for hepatocelluar damage than serum alanine aminotransferase in hypertensive disorder of pregnancy. Am J Obstet Gynecol 1998; 178, (1):161–5.

10. Elad Mei-Dan, Arnon Wiznitzer, Ruslan Sergienko, Mordechai Hallak, Eyal Sheiner. Prediction of preeclampsia: liver function tests during the first 20 gestational weeks. J Mat-Fetal Neonatal Med 2013 ;26(3):250–253

11. Rath W, Faridi A, Dudenhausen J.W.HELLP Syndrome. J Perinat Med 2000; 28 (4):249–60.

12. Girling J, C. Dow E, Smith J.H. Liver function tests in pre-eclampsia: importance of comparison with a reference range derived for normal pregnancy. Br J Obstet Gynaecol 1997; 104(2):246-50.

13. Makuyana D, Mahomed K, Shukusho F.D, Majoko F. Liver and kidney function tests in normal and pre-eclamptic gestation-a comparison with non-gestational reference values. Cent Afr J Med 2002; 48, (5):55-9, 2002.