Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 8 (8): 722-727
15th December, 2008

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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Serum B-hCG Levels in Diagnosis and Management of Preeclampsia

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The aim of this study was to determine the correlation of serum BhCG level and preeclampsia and evaluate its utility as a diagnostic test. Sixty-six hypertensive pregnant patients, who had been hospitalized and 66 normotensive pregnant women who attended the outpatient perinatology clinic in Imam Khomeini Education and Research Hospital Sari, Iran between April 2007 and April 2008 were enrolled in the study. The patients who had a history of chronic hypertension, diabetes, other chronic disease or smoking and twin pregnancy were excluded. Subjects were matched for gestational age, maternal age and BMI. The serum concentration of B-hCG were measured by chemiluminescence (Liaison Germany). The data were analyzed with usage Student t-test and chi-squire. $p<0.05$ was considered significant. Among 66 women in case group 53% had mild and 46% had severe preeclampsia. The mean of maternal serum BhCG level in patients with preeclampsia was significantly higher than in the controls ($p = 0.002$). In mild preeclampsia the mean of serum BhCG level was greater than that for severe preeclampsia but this difference was not significant ($p = 0.2$). In preeclamptic group with gestational age of 26-30 weeks ($n = 4$) the mean of BhCG level differed from normotensive one ($n = 6$) ($p = 0.8$). Between 31-40 week the mean of BhCG levels in the hypertensive ($n = 62$) and control ($n = 60$) groups were 31240.4±25690.7 and 17387.9±13661 mIU mL^{-1} ($p = 0.04$). In this study, the sensitivity and specificity of BhCG as diagnostic test in preeclampsia was 68 and 63% and the sensitivity and specificity of BhCG for differentiation between mild and severe disease was 68 and 66%. The utility of elevated BhCG as diagnostic test for diagnosis and management of preeclampsia is limited.

Key words: Prediction of preeclampsia, maternal serum beta-hCG, vascular remodeling, pregnancy induced hypertension

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INTRODUCTION

Preeclampsia is a human pregnancy-specific disorder that adversely affects the mother and fetus (Sibai *et al*., 2005; Grujiae and Milasinoviae, 2006; Khan *et al*., 2006). The incidence of preeclampsia is between 5-11% of pregnancies and affects mainly women under 20 years of age (Kang and Struben, 2008).

Preeclampsia is diagnosed by the new development of hypertension (≥140 mmHg), significant proteinuria and remission of these signs after delivery (Leeman and Fontaine, 2008).

Although, the exact pathophysiologic mechanism is not clearly understood, but preeclampsia is primarily a disorder of endothelial function with associated vasospasm (Brodszki *et al*., 2008; Hayman *et al*., 2000; Roberts, 2000). About 18 years ago Roberts *et al*. (1990) proposed that maternal endothelial cell dysfunction is the key event resulting in the diverse clinical manifestation of preeclampsia. It can decrease utero-placental blood flow about 30-50% compare to the normal pregnancy (Chavarria *et al*., 2003). The mechanisms involved in induction of endothelial cell dysfunction are poorly understood, but evidence points to the placenta as a key source of the factors that lead to the maternal endothelial cell dysfunction in preeclampsia (DiFederico *et al*., 1999). HCG is a glycoprotein with lipid structure that expressed in trophoblast and various malignant tumors. Physiological concentration of hCG significantly increased *in vitro* capillary formation and migration of endothelial cells in a dose dependent manner and has a novel function in uterine adaptation to early pregnancy (Zygmunt *et al*., 2002). Because the possible role of hCG in pathophysiology of preeclampsia is not well understood and changes in it's level can reflect the placental reaction to the preeclampsia, we are promoted to determine correlation of serum concentration of BhCG and preeclampsia.

MATERIALS AND METHODS

Sixty-six hypertensive pregnant patients, who had been hospitalized and 66 normotensive pregnant women who attended the outpatient perinatology clinic in Imam Khomeini Education and Research Hospital Sari, Iran between April 2007 and April 2008 were enrolled in the study. Non of them had a history of chronic hypertension, diabetes, other chronic disease or smoking. Also the women with twin pregnancy were excluded. This investigation was designed as a prospective study. Subjects were matched for gestational age, maternal age and BMI. The criteria for severe preeclampsia were systolic blood pressure ≥160 mmHg or diastolic ≥110 mmHg and proteinuria ≥5 g in 24 h. In addition any patient with oliguria (<30 mL in h), cerebral or visual disturbance, epigastric pain pulmonary edema, or abnormal platelet count and liver function profile was included in severe preeclampsia. The subjects in control groups were followed to term and who developed preeclampsia (BP≥140/90 mmHg and proteinuria ≥+) or IUGR (±1 SD of average at term) were excluded. The venous blood samples were obtained from the subjects and allowed to clot at room temperature and aliquots of serum by centrifugation. Serum were collected and stored until analysis. Serum levels of B-hCG were measured by chemiluminescence (Liaison, Germany).

The data were analyzed with usage of SPSS (11) software. The two groups were compared for statistical calculation, with Student t-test and chi-squire. $p<0.05$ was considered significant.

RESULTS

Serum BhCG level measured in 66 preeclamptic and 66 healthy pregnant women. As shown in Table 1 there was no difference between two groups in the term of mean age, gestational age and BMI.

In the preeclamptic group, the mean of systolic blood pressure were (147.5±12.03) and in the controls were (117.11) ($p = 0.000$).

Also, in the preeclamptic group, the mean of diastolic BP were (93.8±10) and in the controls were (65±11.63) ($p = 0.000$).

Among 66 women in case group, 35 women had mild preeclampsia (53%) and 31 women had severe one (46%). The mean of maternal serum BhCG levels in patients with preeclampsia was 34691±38760 mIU mL^{-1} that is significantly higher than in the controls (18111.7±15147.9 mIU mL^{-1}) ($p = 0.002$) (Fig. 1). The minimum values of BhCG in preeclamptic group were 1467 mIU mL^{-1} and the maximum values were 140477 mIU mL^{-1}. Also the lower limit of BhCG values in controls were 1483 mIU mL^{-1} and the upper limit values were 76683 mIU mL^{-1}. In mild preeclampsia the mean of serum BhCG level was (28859±42986 mIU mL^{-1}) and in severe preeclampsia was (41275.6±32807.1 mIU mL^{-1}) ($p = 0.2$) (Fig. 2). In addition we compared the mean level

Table 1: Subject data in preeclampsia and controls

	Group (n = 66)		
Variable	Preeclampsia	Control group	p-value
Maternal age (year)	27.26±5.86	27.06±5.01	0.2
Gestational age (week)	35.50±2.8	34.40±2.9	0.5
BMI	31.77±4.55	30.38±4.27	0.4

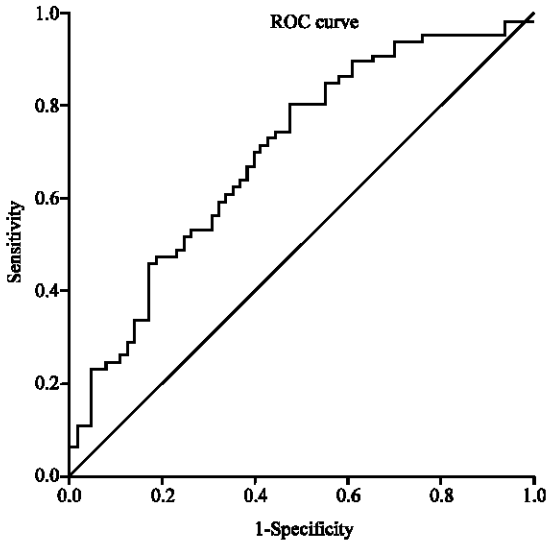

Fig. 1: The sensitivity and specificity level of BhCG between preeclamptic women and healthy pregnant women

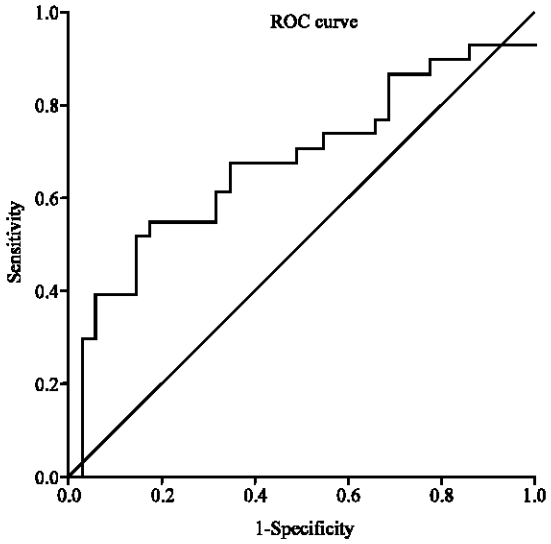

Fig. 2: The sensitivity and specificity level of BhCG between mild and severe preeclamptic groups

of BhCG in patients with mild and severe preeclampsia with controls separately. This comparison revealed that there is statistically significant difference between severe preeclampsia and control group, ($p = 0.001$) but this difference was not statistically significant between mild preeclampsia and controls ($p = 0.18$). The subjects were further divided according to the gestational age (26-30 and 31-40 weeks). Patients with the gestational age of 26-30 weeks in preeclamptic group ($n = 4$) demonstrated a mean BhCG level greater than that of normotensive one ($n = 6$) but this difference was not statistically significant (28079.5 ± 29064.5 m IU mL^{-1}) vs. (25349.6 ± 26677.2 m IU mL^{-1}) ($p = 0.8$). Between 31-40 week the mean of BhCG levels in the hypertensive ($n = 62$) and control ($n = 60$) groups were 31240.4 ± 25690.7 and 17387.9 ± 13661 m IU mL^{-1} ($p = 0.04$). Receiver operating characteristic curve identified that with cut off point of 20153 mIU mL^{-1}, the sensitivity and specificity of BhCG as diagnostic test in preeclampsia is 68 and 63% and the sensitivity and specificity of BhCG for differentiation between mild and severe disease is 68 and 66% with cut off point of 25664 mIU mL^{-1}.

DISCUSSION

One of the most remarkable features of human placental development is the extensive modification of the maternal vasculature by trophoblast cells which are by definition of fetal origin. These events occur in the first half of pregnancy and are considered in detail because of their importance in the understanding of utero placental blood flow in normal pregnancy and labor. They are also important in pathological conditions such as preeclampsia and intrauterine growth restriction (Cunningham *et al*., 2005).

The development of these utero placental vessel modifications has been described in waves. The first wave occurs before 12 weeks post fertilization and consists of invasion and modification of the spiral arteries of the deciduas, reaching its border with myometrium. Between 12 to 16 weeks post fertilization, the second wave occur. This involves invasion of the intra myometrial parts of the spiral arteries, converting narrow-lumen, muscular spiral arteries in to dilated, low resistance utero placental vessels (Kaufmann *et al*., 2003; Klima, 2000; Lyall *et al*., 2001). These physiological changes are required to meet the demands of the rapidly growing feto placental unit during the later stage of gestation. Genesis of preeclampsia is clearly related to deficient trophoblast invasion and failure of uterine artery remodeling (McMaster *et al*., 2004; Fisher, 2004; Baumwell and Karumanchi, 2007). Defective spiral artery remodeling in preeclampisa likely results in reduced utrero placental perfusion and foci of placental hypoxia or ischemia (Fisher, 2004; Stennett and Khalil, 2006; Alexander *et al*., 2002). Many of the ultra structural changes of preeclamptic placental tissue resemble alterations in placental tissue when placed in hypoxic organ culture (Genbacev *et al*., 1996; Tominaga and Page, 1966). Angiogenesis and vascular remodeling are crucial processes in embryo implantation and normal

development. HCG is a major trophoblastic peptide hormone that is responsible for numerous pregnancy-related and pregnancy-maintaining processes and that exhibits a dramatically increasing plasma concentration during the first trimester (Perrier d'Hauterive *et al*., 2007; Risuparp *et al*., 2001). Study from Zygmunt *et al*. (2002) revealed that hCG/LH receptors are present in the endothelium and smooth muscle of blood vessels *in vivo* that their expression level is significantly increased in the intra myometrial segment. In addition, the fact that hCG/LH receptors are up regulated by progesterone in the second phase of the menstrual cycle strongly indicated a role for the hCG-hCG/LH receptor complex in uterine adaptation during implantation and placentation (Lei *et al*., 1992; Toth *et al*., 1994; Perrierd' Hauterive *et al*., 2007). Zygmunt *et al*. (2002) indicated that hCG has a direct angiogenic function on hCG/LH receptor-expressing in uterine endothelial cells. Their findings not only support the hypothesis that hCG may have an important regulatory role in angiogenesis and vascular function in the female reproductive tract, but also indicate that hCG could be involved in the placental vasculogenesis and angiogenesis in early stages of placental development, as high hCG concentration were detected in fetal tissue of early pregnancy. Data strongly argue in favor of an important influence of hCG in mediating the induction of uterine angiogenesis during the first trimester in pregnancy. Besides this direct angiogenic activity, hCG can induce the expression of other angiogenic factors, such as VEGF, in macrophages, thereby indirectly contributing to neovascularisation as well (Zygmunt *et al*., 2002). There is also evidence that hCG has strong vasodilatory actions on uterine arteries (Hermsteiner *et al*., 1999, 2002). As well as on the human ovarian vasculature (Jauniaux *et al*., 1992). Therefore hCG has a potent angiogenic stimulus in the feto-maternal unit.

In particular recent studies have shown that hCG may be involved in tumor development via suppression of apoptosis (Butler *et al*., 2000; Yu *et al*., 2007; Matsubara *et al*., 2000). The angiogenic function of hCG could very well be associated with a suppression of apoptosis in endothelial cells. In this study with the measurement of BhCG level in 66 preeclamptic patients and 66 healthy pregnant women the relationship between BhCG concentration and preeclampsia was evaluated.

In keeping with other investigator (Gurbuz *et al*., 2004; Vaillant *et al*., 1996; Casart *et al*., 2001) we also found that the mean BhCG value of women with preeclampsia, was statistically significantly higher than healthy pregnant women ($p = 0.002$). Although, in this study BhCG concentration was positively correlated with disease severity. So, that when the mean BhCG values of the patients with mild and severe preeclampsia were compared together, this value was higher in severe preeclampsia but this difference was not statistically significant ($p = 0.2$).

Data from the Lambert's population indicated that BhCG concentration in preeclamptic patients are higher than controls and this difference was more obvious in moderate and severe disease (Lambert-Messerlian *et al*., 2000). In their study there was not statistically significant difference between BhCG level in mild preeclampsia and controls. Similar to their study, however, this findings showed that, BhCG level in severe preeclampsia differed from normal pregnancy and this difference is statistically significant (0.001) while in mild preevlampsia, although, BhCG values were higher than controls, but this difference was not statistically significant ($p = 0.18$). Ramsey and Parker (2003) showed in a prospective study that BhCG level is significantly higher in preeclamptic patients. In their study 131 of the 132 normotensive women had serum BhCG levels between 1000-4000 mIU mL^{-1} and the maximum number of normotensive women had serum BhCG levels between 2000 and 3000 mIU mL^{-1}. Data from our population indicated that there was severe overlap between BhCG levels in two groups so, that we were unable to determine an exact cut off with high sensitivity and specificity for diagnosis of preeclampsia, or mild versus severe disease.

In current study the gestational age of 4 patients in case group and 6 women in controls were ≤30 w and when BhCG values of them compared together the difference was not statistically significant ($p = 0.8$). While in preeclamptic patients with gestational age of >30 w this difference was significant ($p = 0.04$). This finding was correspond to obtained results of Moodly's survey (Moodley *et al*., 1995). In contrast with us Simon Shenhav *et al*. (2002) observed that the mean BhCG level in the early onset group was significantly higher than in the late onset group. They related this finding to the severity of endothelial cell dysfunction in early onset disease.

Data from Huppertz (2008) suggested that early and late onset preeclampsia have different etiologies and therefore a different clinical expressions. In late onset preeclampsia the behavior of the uterine arteries are normal or only slightly altered but in the early onset disease vascular damages are more prominent. It seems likely that in this condition placenta is unable to exert any compensatory effect and thereby BhCG level will be declined. In the opinion this point is need to more attempt and perhaps, it is necessary to compare between serum

BhCG concentration in early onset preeclampsia and late onset disease with more patients. At this time, according to the results of this study the utility of elevated BhCG level as a diagnostic test for preeclampsia is limited and need to be clarified in future investigations.

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