Could Preeclampsia Affect The Maternal Serum Chorionic Gonadotrophin and Plasma Adenosine Deaminase Levels?

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Abstract: The current work aimed to study the effect of preeclampsia on maternal serum level of beta subunit of human chorionic gonadotropin and maternal plasma level of adenosine deaminase. Ninety pregnant women with gestational age 24 - 26 weeks were selected for this study, they were classified into three groups: group 1 consists of 30 women with normal pregnancy, group 2 consists of 30 patients with mild preeclampsia and group 3 consists of 30 patients with severe preeclampsia. Maternal serum level of beta subunit of human chorionic gonadotropin, and maternal plasma adenosine deaminase level were measured. Maternal serum level of beta subunit of human chorionic gonadotropin was significantly higher in severe preeclampsia compared with the mild preeclampsia group and normal pregnancies. Maternal plasma adenosine deaminase level was significantly higher in the severe group compared with the mild preeclampsic and normal groups. Maternal serum level of beta subunit of human chorionic gonadotropin and maternal plasma level of adenosine deaminase might be useful as markers of the severity of preeclampsia.

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1. Introduction

Preeclampsia (PE) remains a major cause of prenatal morbidity and mortality worldwide (Harskmp et al., 2007). Early identification of pregnant women at risk for **preeclampsia** is a priority to implement preventive measures (Giguère et al., 2010). The etiology and pathogenesis of PE are not fully understood, but two important components have been identified: the role of trophoblast cells and an accelerated maternal systemic response to trophoblastic tissue (Sargent et al., 2003).

The production *of* human chorionic gonadotropin (hCG) by the placenta in early pregnancy is critical for implantation and maintenance of the blastocyst (Reisinger et al., 2007). Since it is postulated that PE is likely to be a trophoblastic disorder, it may be essential to investigate the pathologic and secretory reaction of the placenta to understanding the disease. Twin pregnancy and molar pregnancy produce higher levels of B-hCG and they are associated with a higher incidence of PE than uncomplicated singleton pregnancy (Long and Oat, 1987).

Adenosine deaminase (ADA) is a cytosolic enzyme, which has been the object of considerable interest mainly because a congenital defect in this enzyme in humans causes severe combined immunodeficiency disease (Franco et al., 1987). ADA participates in purine metabolism where it degrades either adenosine or 2-deoxyadenosine producing inosine or 2'-deoxyinosine respectively. Further metabolism of these deaminated nucleosides leads to hypoxanthine. ADA could have an extraenzymatic activity through binding directly to different cell surface molecules including CD-26 (a lymphocyte activation marker), so it is regarded as a cellular inflammatory indicator. ADA presents in all human tissues with highest level in lymphoid system. It may play a central role in the differentiation and maturation of the lymphoid system (Herrera et al., 2001).

The objective of the present study is to evaluate the correlation between maternal serum B-hCG level, maternal plasma ADA level and severity of PE which may reflect a different trophoblastic severity response of the disease.

2. Patients and Methods

This study was carried out on 90 pregnant women classified into 3 groups: group 1 consists of 30 normotensive non proteinuric pregnant women; group 2 consists of 30 women with mild PE; and group 3 consists of 30 women with severe PE. Women were recruited from the Obstetrics and Gynecology Outpatient Clinic of Benha University Hospital from June 2009 to June 2010. Inclusion criteria were singleton fetus, normal fetal anatomy, non-smoker and gestational age of 24-26 weeks

assessed by ultrasonography. Women with chronic hypertension, systemic disease as diabetes mellitus, collagen disease and recent infections were excluded.

Mild PE was defined as a combination of (1) systolic blood pressure (SBP) ≥ 140 and < 160 mm Hg or a diastolic blood pressure (DBP) ≥ 90 and < 110 mm Hg on two consecutive measurement six hours apart (2) proteinuria of ≥ 0.3 g and < 2 gm per 24 hours urine specimen or > 1 and < 3 + on dipstick testing of two random urine samples four hours apart. Severe PE was defined as (1) SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on two consecutive measurement at least six hours apart on bed rest and (2) proteinuria ≥ 2 gm per 24 hours urine specimen or ≥ 3 + on dipstick testing of two random urine sample four hours apart. In addition, any patient with oliguria (>400 ml in 24 hours), cerebral or visual disturbances, epigastric pain, pulmonary edema, abnormal edema, abnormal platelet count or abnormal liver function profile was included in the severe PE group (ACOG, 2002).

- For β-hCG estimation, the random venous 2cc blood samples were centrifuged at 2000 g for 10 minutes at 4 ºC. Sera were collected and stored at -20ºC until analysis. Serum level of (β-hCG) were measured by enzyme immunoassay according to Ozturk, et al., 1988 using free beta-hCG ELISA Kit (purchased from IBL - Hamburg GmbH, Flughafenstr, 52A, D-22335 Hamburg, Germany) and ELISA Reader (SLT-Spectra, Mode-III, Austria).
- For ADA estimation, the random heparinized 2cc blood samples were centrifuged for 10 minutes at 3000g and the plasma was separated and frozen at –70ºC until analyzed. (ADA) activity was measured spectrophotometrically (Spectronic 3000 Array, Milton-Roy, USA) in the maternal plasma using the method described by Giusti and Galanti, 1984, based on direct measurement of the ammonia produced when ADA acts in excess of adenosine.

Statistical analysis:

The data were reported as mean and standard deviation (SD). For statistical analysis, analysis of variance (ANOVA) and correlation coefficient (r) were used and p values < 0.05 were considered statistically significant. Statistical package for social science (SPSS) version 10 was used for data analysis.

3. Results

The mean maternal age was significantly higher in group 3 than in group 2 and group 1($p<0.05$). The parity was lower in group 3 than in group 2 and group 1 but the difference was not statistically significant. Maternal serum β -hCG was significantly higher ($p<0.05$) in group 3 than in group 2 and group 1. Maternal plasma ADA was significantly higher ($p < 0.05$) in group 3 than in group 2 & 1 (table 1).

The maternal age, maternal serum levels β-hCG and maternal plasma ADA showed a significant positive correlation with SBP/DBP and albuminuria. Parity showed significant negative correlation with SBP/DBP and albuminuria in group 2 (Table 2).

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Table (1): Characteristics of study participants in the 3 groups

Groups / Data	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p
Age (y)	**25.4 ± 0.27**	**27.73 ±0.36**	**31.20 ±5.54**	**<0.05**
Parity	**3.07 ± 0.30**	**2.60 ± 0.32**	**2.0 ± 0.32**	**<0.05**
β-hCG (mIU/ml)	**16708.67 ± 1380.1**	**22504.67 ± 1161.40**	**29306.0 ± 1283.56**	**<0.05**
ADA (IU/l)	**8.99 ± 0.46**	**12.95 ± 0.69**	**14.95 ± 0.52**	**<0.05**

β-hCG = maternal serum beta subunit of human chorionic gonadotropin.
ADA = maternal plasma adenosine deaminase p<0.05= significant.

Table (2): Correlation Coefficient (r) between systolic, diastolic blood pressure albuminuria, age, parity, maternal serum β-hCG, maternal plasma adenosine deaminase (ADA) in group 2.

Parameters / Data	Systolic blood pressure (SBP)		Diastolic blood pressure(DBP)		Albuminuria	
	r	p	r	p	r	p
Age (y)	0.92	<0.05	0.53	<0.05	0.85	<0.05
Parity	-0.88	<0.05	-0.54	<0.05	-0.84	<0.05
β-hCG (mIU/ml	0.92	<0.05	0.58	<0.05	0.84	<0.05
ADA (IU/l)	0.92	<0.05	0.54	<0.05	0.85	<0.05

β-hCG = maternal serum beta subunit of human chorionic gonadotropin.
ADA = maternal plasma adenosine deaminase p<0.05= significant.

Table (3): Correlation Coefficient (r) between systolic, diastolic blood pressure albuminuria, age, parity, maternal serum β-hCG, maternal plasma adenosine deaminase (ADA) in group 3.

Parameters / Data	Systolic blood pressure		Diastolic blood pressure		Albuminuria	
	r	p	r	p	r	p
Age (y)	0.88	<0.05	0.88	<0.05	0.83	<0.05
Parity	-0.70	<0.05	-0.63	<0.05	-0.89	<0.05
β-hCG (mIU/ml	0.89	<0.05	094	<0.05	0.79	<0.05
ADA (IU/l)	0.91	<0.05	0.83	<0.05	0.71	<0.05

β-hCG = maternal serum beta subunit of human chorionic gonadotropin.
ADA = maternal plasma adenosine deaminase p<0.05= significant.

Discussion

The normal placenta differentiates during pregnancy with dominance of cytotrophoblast in early gestation and syncytiotrophoblast in late gestation. It is well known that cytotrophoblasts are undifferentiated stem cells and that syncytiotrophoblasts are differentiated from the cytotrophoblast (Kliman, et al., 1987).

Although the mechanism of regulation of gestational hCG remains largely unknown, it is generally accepted that hCG is secreted only by the syncytiotrophoblast (Fox, 1970). Remzi et al showed that early placental vascular damage leading to decreased oxygen supply might result in increased hCG production by hyperplasic cytotrophoblastic cells (Remzi, et al., 2000). Also, hCG production has been shown to increase when normal placental villi in organ culture were maintained under hypoxic condition. Typically the placenta is the affected tissue in PE (Correa, et al., 2007). In PE, placental pathologic examination reveals focal cellular necrosis in the syncytiotrophoblast and increased mitotic activity with cellular proliferation in the cyto-trophoblast. In addition, the proliferating cytotrophoblast in severe PE is rapidly transformed into syncytiotrophoblast within 72 hour (Hoshina, et al., 1982).

In recent years, many studies have been conducted to determine the relation between maternal serum hCG levels and subsequence development of PE. Most studies indicated that an unexplained elevation of maternal serum B-hCG is significantly correlated with the occurrence of PE (Benn et al., 1996 and Luckas et al., 1998). By contrast Morssink et al., (1997_a) and Pouta et al., (1998) demonstrated no association, while Ashour et al., (*1997)* showed that significant association was reached only among multiparous women.

Regarding the relation between the levels of maternal serum B-hCG and the severity of PE, Hsu et al demonstrated that a significantly raised serum B-hCG level was only associated with severe PE (Hsu et al., 1994). Long-chien et al demonstrated multiple determining factors for severe PE including elevated mid-trimester B-hCG, multiparity, advanced maternal age and high basal body mass index; BMI (Long-chien et al., 2000). This study showed a significant positive correlation between maternal serum β-hCG and the severity of PE. However significant negative correlation was found between the severity of PE and parity. This agrees with Basirat et al and may suggest an earlier occurrence of pathologic changes of the placenta among women at risk for later development of severe PE (Basirat et al., 2006).

The enzyme ADA is mainly located in haemopoeitic cells such as Th1 cells, monocytes and macrophages. Beside ADA, Th1 cell produce the basic proinflammatory cytokines interleukin (IL2), tumor necrosis factors & (TNF-α) and interferon-α

(INF-α). Insufficient arterial remodeling and shallow trophoblastic invasion are characteristic placental pathologies in PE (Merviel et al., 2004). An unbalanced inflammatory reaction at the placental implantation site is a proposed causative mechanism. There is biological and histological evidence supporting the existence of a proinflammatory reaction including Th1 cytokine dominance within and around the spiral arteries that separate them from trophoblast cells (Sargent et al., 2003). PE is characterized by enhanced cell- mediated immunity, thus serum ADA activity tends to increase in PE (Yoneyama et al., 2002).

Initial studies of maternal and fetal plasma ADA demonstrated a significant increase in PE patients, compared with normal pregnancy [(24)]. Kafkasli et al demonstrated higher increase in ADA activity in placental tissue compared with maternal or fetal plasma level in both mild and serve PE. This study shows a significant positive correlation between maternal plasma ADA and severity of PE (Kafkasli et al., 2006).

It could be concluded that maternal serum β-hCG and maternal plasma ADA increase in cases of mild and severe PE.

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