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RESEARCH ARTICLE

ASSOCIATION OF SOME SERUM BIOMARKERS TO SEVERE PRE-ECLAMPSIA A PROSPECTIVE CONTROLLED CLINICAL STUDY

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ABSTRACT

Background: Pre-eclampsia has significant impacts on maternal and fetal health. It is a leading cause of maternal mortality in both developed and developing countries. Early prediction of the disease would help in determining those patients who were more likely to benefit from interventional measures**. Objective**: to evaluate association of some serum biomarkers (calcium, creatinine, and uric acid) to severe pre-eclampsia. **Patients and methods:** 50 apparently healthy primigravidae of attendants of antenatal care clinic of the department of obstetrics and gynecology, Al-Azhar University, Assiut- Egypt, during the period from January 2019 till July 2019 were recruited for the study, 25 normal pregnant women as controls (group I) and 25 pregnant women who developed severe pre eclampsia (group II) later during follow up . The blood samples were collected and analyzed for serum calcium, creatinine and uric acid level during booking visit and repeated later in third trimester or when suspicious signs or symptoms developed during ANC visits. **Results**: serum calcium levels was significantly lower (7.93± 0.12mg/dl vs. 8.76 ± 0.22 mg/dl, $p < 0.05$ for severe pre-eclampsia and control groups respectively), serum uric acid were significantly higher (7.42± 1.35mg/dl vs. 5.12 ± 1.34mg/dl, $p < 0.001$ for both groups respectively), serum creatinine was statistically non significant between both groups ($p > 0.05$). **Conclusion**: hypocalcaemia and hyperurecimia were associated with pre-eclampsia and might be attributed to the development and progression of the disease. **Recommendation:** Low serum Ca and elevated uric acid levels can be used as early predictors for severe preeclampsia

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INTRODUCTION

Internationally, preeclampsia is defined as new-onset gestational hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) associated with new-onset of at least one of proteinuria, maternal organ dysfunction (liver, neurological, haematological, or renal involvement), or uteroplacental dysfunction at or after 20 weeks' gestation (National Guideline Alliance, 2019). It is important to note that preeclampsia may develop for the first time intrapartum or postpartum. Super-imposed preeclampsia can also be diagnosed in women with chronic hypertension who develop new onset proteinuria, maternal organ, or uteroplacental dysfunction consistent with preeclampsia (Brown, 2018). Pre eclampsia have a 2-4 fold increased risk of long-term hypertension, a doubling of the risk of cardiovascular mortality, and a 1.5-fold increased risk of stroke. For the fetus, intra-uterine growth restriction (IUGR), preterm birth (iatrogenic), oligohydramnios, placental abruption, fetal distress, and fetal death in utero (Madazli *et al*., 2014). The pathophysiological mechanism originates in the placenta, starting with inadequate cytotrophoblast invasion of the spiral arteries, leading to mal-adaptation of maternal spiral arterioles with an increased vascular resistance of the uterine artery and a decreased perfusion of the placenta (Wang, 2009). Preeclampsia is a leading cause of maternal mortality in developing countries, with estimates of >60,000 maternal deaths/year (World Health Organization, 2005).

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Various studies have evaluated several biochemical parameters during the first or second trimester of pregnancy, as potential predictors of pre-eclampsia. Plasma concentrations of creatinine in pre-eclampsia have been shown to be significantly higher than in the normotensive subjects (Vafaei *et al*., 2015). Uric acid is a marker of oxidative stress, tissue injury and renal dysfunction and therefore may be useful in the prediction of complications of PE. The hyperuricemia is believed to result from the decreased renal excretion that occurs as a consequence of the preeclampsia but this result is probably also increased production secondary to tissue ischemia and oxidative stress (Martin, 2010). Calcium also has been suggested to have a role in PE. Role of calcium supplementation in reducing hypertensive disorders in pregnancy can possibly be explained by reduction in parathyroid calcium release and intracellular calcium concentration, thereby reducing smooth muscle contractility and promoting vasodilatation (Mohieldein *et al*., 2007). It is important therefore to identify women at high risk of developing the disease early in pregnancy not only to facilitate selective recruiting of those at increased risk for pre-eclampsia but also to help in determining those patients who were more likely to benefit from interventional measures should a therapeutic intervention prove successful. However, the role and status of serum calcium, serum creatinine and serum uric acid in pregnant women are still being discussed (Kumar, 2019).

Objectives: to evaluate the association of some serum biomarkers, calcium, creatinine, and uric acid) to severe pre-eclampsia.

PATIENTS AND METHODS

This is a prospective controlled clinical study conducted for 50 attendants of antenatal care clinic of the department of obstetrics and gynecology, Al-Azhar University, Assiut- Egypt, during the period from January 2019 till July 2019. The study started by 60 participants, 10 of them failed to complete the study after enrollment the remaining 50 patients were then enrolled, 25 normal pregnant women as controls (group I) and 25 pregnant women with severe pre eclampsia (group II). A written consent were obtained from all participants in the study

Inclusion criteria: 20-38 years old, healthy, primigravidae, in second half of pregnancy, who were normotensive before 20th week of pregnancy during antenatal care follow up then either developed severe PE or remained normotensive throw ought pregnancy were included in the study

Diagnosis of Sever PE depended on National Guideline Alliance; 2019 (1)

- New-Onset Gestational Hypertension at or after 20 Weeks' BP of at least 160mmHg systolic or 110 mmHg or more measured on two occasions 6 hours apart. *Accompanied by one or more of the following new-onset conditions:*
- proteinuria of at least 3 g per 24 hours, or at least 3+ on dipstick testing.
- Renal complications: Acute Kidney Injury (creatinine ≥ 90 umol/L)
- Liver complications Elevated transaminases, with or without right upper quadrant of epigastric abdominal pain
- Neurological complications: Eclampsia, altered mental status, blindness, stroke, clonus, severe and persistent visual scotomata
- Haematological complications: Thrombocytopenia (platelet count < 150000/μL, disseminated intravascular coagulation, haemolysis)
- Uteroplacental dysfunction: Fetal growth restriction, abnormal umbilical artery Doppler wave form analysis or stillbirth

Exclusion criteria: multiple gestations, chronic hypertension, chronic renal disease, cardiovascular disease, collagen vascular disease or thyrotoxicosis.

MATERIALS AND METHODS

At booking visit, a complete clinical history was taken from each participant. This was followed by a complete physical examination (general, abdominal) and ultrasound examination.

At booking visit, a complete clinical history was taken from each participant. This was followed by a complete physical examination (general, abdominal) and ultrasound examination. Assessment of the lower limb for edema. The weight and height of the patients were measured and the blood pressure taken twice on the right arm in the sitting position with the patient at rest using a mercury sphygmomanometer with an appropriate cuff placed at her heart level, then venous serum samples were collected while the patients in the supine position prior to their commencement to intravenous therapy. Blood samples were collected under aseptic precautions in plain container then sent for complete blood count, serum calcium, serum creatinine, serum uric acid assessment plus routine investigations. Uric acid estimation was done by Uricase Peroxidase Method while total calcium estimation was done by Arsenazo III end point method. Serum urea and creatinine, Serum electrolytes (Na+ & K+), serum ALP, ALT , AST, albumin, total and direct bilirubin were assessed to rule out renal & liver disease. All investigations were done at booking visit then repeated at 28 wks of gestation or when suspicious signs or symptoms developed.

Statistical analysis: data was collected, tabulated and statistically analyzed using SPSS (statistical package for social science version 12). Descriptive data were reported as frequency, percentage, mean and standard deviation (S.D.), for the comparison of result Student t-test and chi-Square were used. A $p < 0.05$ was considered significant.

RESULTS

Table (1) shows socio-demographic and clinical characteristics of the studied groups. There was no statistically significant difference between both groups as regard to age or BMI (p>0.05). There were statistically significant differences in the mean gestational age, systolic and diastolic BP, lower limb edama and symptomes of preecalmpsia (p<0.01). Table (2) shows laboratory findings in the study groups, no statistically significant difference was present in platelet count, hematocrit value or serum creatinine levels (p>0.05). On the other hand serum calcium was lower and serum uric acid levels was significantly higher in PE group than normal control group (p<0.05)

Table 1. Socio-demographic and clinical characteristics of the studied groups

	Group I (n=25)	(Group II) (n=25)	p
Socio-demographic			
• Maternal age (yrs)	19.0± 3.721	18.9± 2.674	>0.05
• Gestational age (wk)	38.2±2.0	35.1±1.32	0.01
• BMI (kg/m^2)	26.42 ± 6.24	27.48 ± 5.37	>0.05
signs			
Blood pressure:			
• Systolic BP (mmHg)	116.0+11.6	167± 23.5	<0.001
• Diastolic BP (mmHg)	78.0± 8.54	110.0± 9.453	<0.001
• Lower limb edema	10(40%)	22(88%)	<0.0001
Symptoms*			
• Headache	3(12%)	22 (88%)	<0.001
• Face& hand puffness	2(8%)	20(80%)	
• Nausea and vomiting	0	15(60%)	
• Vision problem	0	17(68%)	
• seizure	0	1 (4%)	

Values are given as mean ± SD
Values are given as no.% unless otherwise mentioned

Table 2. Laboratory characteristics of the studied groups

	Group I (n=25)	(Group II) (n=25)	p
Platelet count (*10) ^{3}	235.17 ± 75.2	230.27± 57.3	>0.05
Hematocrit (%)	36.34+± 3.12	35.65 ± 3.16	>0.05
Serum creatinine (mg/dl)	0.92 ± 0.22	0.93± 0.12	>0.05
Serum calcium (mg/dl)	8.76 ± 0.22	7.93± 0.12	< 0.05
Serum uric acid (mg/dl)	5.12 ± 1.34	7.42± 1.35	<0.001

Values are given as mean ± SD

DISCUSSION

Pre-eclampsia has been considered as a disease of unknown pathophysiology. Numerous etiologies have been put forward in light of this serious condition of pregnancy. Altered concentration of various trace elements has been reported during pregnancy (Sirajwala; 2013 and Abdellah, 2014). In the present study, there was no statistically significant difference between both groups as regard to age or BMI (p>0.05). On the other hand the mean gestational age was significantly lower (35.1±1.32 vs 38.2±2.0 wks p <0.01), systolic and diastolic BP, lower limb edama and symptomes of preecalmpsia were significantly higher in PE group vs. Control group (p<0.01). No statistically significant difference was present in platelet count, hematocrit value or serum creatinine levels (p>0.05). On the other hand serum calcium was lower and serum uric acid levels was significantly higher in PE group than normal control group (p<0.05). The mean serum calcium level in severe preeclamptic group were 7.93± 0.12 vs. 8.76 ± 0.22 in control group (p<0.05) supported the hypothesis that calcium might be a cause in the development of preeclampsia. These results were in accordance with Dhungana *et al*; 2017 (Dhungana *et al*., 2017) who found in their study on serum level of calcium and magnisum that the mean serum magnesium level of preclampsia (1.83 ± 0.21mg/dl) was lesser in comparison to normal pregnant women (2.03 ± 0.16 mg/dl). Similarly the level of serum calcium level was lower (8.10 ±0.56mg/dl) when it was compared with control (9.59 ±0.62 mg/dl). Also our results were in agreement with many other studies (Sirajwala *et al*., 2013; Abdellah,2014;

Ibrahim, 2013). The effect of serum calcium on changes in blood pressure during preeclampsia could be best explained by the level of intracellular calcium. The increase in intracellular calcium or decrease in serum calcium levels leads to constriction of smooth muscle in blood vessels and subsequent increase in vascular resistance. Ionized calcium is also crucial for synthesis of nitric oxide and prostacyclin and hence calcium deficiency also aggravates oxidative stress. The protective effect of calcium on blood pressure can be explained by the influence of calcitrophic hormones on intracellular calcium. 1, 25-dihydroxyvitamin D stimulates calcium influx in a variety of cells, including vascular smooth muscle cells. As a consequence, 1,25-dihydroxyvitamin D exerts a repressor effect, serving to promote contraction and increase peripheral vascular resistance. Consequently, low calcium diets, which elicit a 1, 25- dihydroxyvitamin D response, would be expected to increase blood pressure (Sirajwala *et al*., 2013).However, our finding about serum calcium was not in accordance to many other authors who found that the mean serum calcium levels in preeclampsia were not different from normal pregnancy (Ingec *et al*., 2006; Bangou, 2016; Ugwuja, 2016). In the present study no statistically significant difference were present between both groups as regard serum creatinine level ($p>0.05$). This result is contradictory to some studies which reported that the mean serum creatinine level in severe preeclampsia was higher than normal pregnancy explained by decreased renal clearance as a result of renal impairment (Sanders *et al*., 1999, Vafaei *et al*., 2015; Dhungana *et al*., 2017;). In the present study, the mean serum uric acid level of PE group was significantly higher than normal pregnant women (7.42± 1.35 vs. 5.12 ± 1.34mg/dl $p<0.001$). The present findings were similar to the findings of previous studies (Mohieldein *et al*., 2007; Sirajwala *et al*., 2013, Dhungana *et al*., 2017 and Kumar, 2019). Kumar *et al* 2019 attributed the elevated serum uric acid levels to decreased renal urate excretion frequently found in women with pre eclampsia. It always has been assumed to be a reflection of disease rather than a cause and it has antioxidant properties that serve to protect from oxidative stress, but it also appears to contribute directly to endothelial dysfunction by its proinflammatory effect. The mechanism of how uric acid in development of hypertension in humans has yet to be elucidated, but evidence suggest that uric acid plays a significant role because uric acid levels correlate with plasma renin activity (Sirajwala, 2013 and Kumar, 2019).

Conclusion

Low serum Ca and elevated uric acid levels are associated with pre-eclampsia and might be attributed to the development and progression of the disease. Thus, these elements along with other serum biomarkers would definitely be helpful in effective management of pre-eclampsia

Recommendation

Low serum Ca and elevated uric acid levels can be uesed as early predictors for preeclampsia.

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