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Role of serum adenosine deaminase and c-reactive protein levels in preeclampsia

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ABSTRACT

Introduction: Preeclampsia is one of the common medical complications during pregnancy and is one of the top five causes of maternal death in the world. Preeclampsia is defined as development of hypertension, proteinuria and edema at or after 20^{th} weeks of gestation. The main aim of this study was to estimate and compare levels of adenosine deaminase (ADA) and C- reactive protein (CRP) in serum of preeclampsia and normotensive pregnant women.

Materials and Methods: This case control study included 120 subjects who were pregnant and in the age group of 19-35 years. 60 preeclampsia patients were taken as cases and 60 age matched healthy primigravida as controls. After obtaining ethical clearance and taking informed consent, ADA and CRP levels were analysed. Serum CRP was estimated by immunoturbidimetric method and ADA was estimated by colorimetric method on a spectrophotometer. Results are expressed as mean±SD. Comparison of two study groups was done using unpaired student's t test. A p value of less than 0.05 was considered significant.

Results: There was significant increase in the serum levels of ADA and CRP in cases of preeclampsia in comparison to normotensive pregnant women.

Conclusion: Elevated levels of serum ADA suggests the role of probable decreased cell mediated immunity in normal pregnancy and increased cell mediated immunity in preeclampsia. Increased CRP levels reflect the inflammatory response in progression of disease. Estimation of ADA and CRP parameters is inexpensive and can be of some diagnostic and prognostic significance in preeclampsia.

1. Introduction

Preeclampsia is a condition characterized by development of hypertension (≥140/≥90 mmHg) and proteinuria (≥0.3g/24h) at or after 20 weeks of gestation in a previously normotensive woman. It is associated with thrombocytopenia, disseminated intravascular coagulation and hepatocellular damage.[1] Preeclampsia is said to be an important cause of both fetal and maternal mortality.[2] In developing countries, due to inadequate prenatal care, preeclampsia is the leading cause of hospital admission of pregnant women to intensive care units and accounts for nearly 50000 maternal deaths per year.[3] Preeclampsia is multifactorial in origin, and recent research has focused on endothelial dysfunction as main abnormality in preeclampsia.[2]

Adenosine deaminase enzyme is useful for the maintenance of immune system and it is also associated with gestation maintenance in humans.[4] Serum ADA activities were less in normal pregnant women in comparison to non-pregnant women indicating its association with decreased cell mediated immunity during normal pregnancy. Also, some studies have indicated that increased serum ADA

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activity is associated with recurrent abortion, hyperemesis gravidarum and preeclampsia conditions where cell mediated immune response plays an important role in their pathogenesis.[5]

C-reactive protein (CRP) is a protein synthesized by the hepatocytes. Its level in blood increases in response to inflammation.Also, plasma CRP levels are increased in cases of acute infection and malignancy.[6] The Endothelial Cell Dysfunction (ECD) and inflammatory processes have recently been implicated in the pathogenesis of preeclampsia. It was further suggested that CRP may be associated with eliciting the inflammatory response mechanism in preeclampsia.[7]

There are very few studies analyzing both ADA and CRP in preeclampsia. So,this study was taken up to assess the clinical utility of serum ADA and CRP as biochemical markers in preeclampsia.The main objectives of the study were to estimate and compare the serum C- reactive protein and adenosine deaminase levels in preeclampsia and normotensive pregnant women.

2. Materials and Methods

This case control study is a prospective study done at outpatient clinic of Obstetrics and Gynaecology department of People's Institute of Medical Sciences, Bhopal between October 2018 to September 2019. A total number of 120 subjects in the age group of 19-35 years were selected for this study based on the inclusion and exclusion criteria. Out of the 120 subjects, 60 preeclampsia patients were assigned as cases and 60 age matched healthy primigravida were included as controls.

2.1. Inclusion criteria

Preeclampsia cases included were diagnosed according to American college of Obstetrics and Gynaecology (ACOG) criteria: "a blood pressure higher than 140/90 mm of Hg, oedema and Proteinuria > 300 mg/24 hours or ≥ 1+ dipstick method after 20th week of gestation".[7] All the controls included were singleton primigravida with gestational age of 28- 40 weeks and had no past history of any medical disorders ,were not in active labor and had normal blood pressure throughout pregnancy.

2.2. Exclusion criteria

Patients with past history of hyperuricemia, diabetes,hypertension, kidney diseases,cardiovascular disease, autoimmune disorders like Systemic Lupus Erythematous, rheumatic arthritis, taken photochemotherapy in the last three months and having fungal or symptomatic infectious diseases were excluded from both the study groups.

2.3. Study procedure

Ethical Clearance was taken from the Institutional Ethical and Research Committee before the start of the study (PCMS/OD/2018/2/05/35). After obtaining informed consent, 5ml of venous blood was collected under aseptic precautions in a sterile plain vacutainer from cases and healthy controls. After centrifugation, serum was separated and levels of CRP and ADA were analysed. Serum adenosine deaminase was estimated by colorimetric method of Giuseppe Guisti and Bruno Galanti[8] manually on a spectrophotometer and serum C-reactive protein was estimated by immunoturbidimetric method[9] using Delta Lab company kit. Blood pressure was measured using sphygmomanometer in sitting position during their routine second trimester antenatal visit. The values recorded along with other tests were used for classifying preeclampsia.

2.4. Statistical analysis

Results are expressed as mean ± standard deviation. Unpaired student's t- test was used to compare between ADA and CRP levels of preeclampsia patients and control groups. A p value of less than 0.05 was considered significant.

3. Results

The mean and standard deviation values of parameters like age, gestational age, systolic and diastolic blood pressure of preeclampsia cases and normotensive primigravida controls are shown in Table I. Age of preeclampsia patients range from 21-35 years whereas age of controls range from 19-33 years. There was significant difference between age of preeclampsia cases and controls (p value < 0.05). Though the gestational age of both preeclampsia patients and controls range from 22-34 weeks, there was slight difference in mean gestational age among both groups. Overall, no significant difference was found between preeclampsia cases and controls with respect to gestational age (p value >0.05).

Systolic blood pressure of preeclampsia patients range from 144-170 mmHg whereas in normal pregnant women, it ranges from 110-126 mmHg. Diastolic blood pressure of preeclampsia patients ranges from 90-110 mmHg whereas in normal pregnant women, it ranges from 78-86 mm Hg. There was significant difference between preeclampsia cases and controls with respect to systolic and diastolic blood pressure (p value <0.05).

In the present study, mean levels of serum ADA and CRP are significantly higher in preeclampsia patients in comparison to normotensive pregnant controls (p<0.001). Though there is high significance between the quantitative values of these parameters, the standard deviation is also high (Table 1).

Table 1: Clinical and biochemical profile of cases and controls

Parameters	Cases (60)(mean ± SD)	Controls (60)(mean ± SD)	p value
Age (in years)	28.1±3.4	25.5±3.1	<0.0001*
Gestational age (in weeks)	30.1±3.0	30.3±3.1	0.720
Systolic Blood Pressure (mmHg)	161.3±6.1	120.5±3.7	<0.0001*
Diastolic Blood Pressure (mmHg)	101.9±5.5	82.2±2.8	<0.0001*
Serum ADA (U/L)	36.1±7.6	14.6±2.5	<0.0001*
Serum CRP (mg/dL)	10.9±5.5	2.0±1.0	<0.0001*

Value <0 001* - high significance

4. Discussion

Preeclampsia is a hypertensive disease of pregnancy affecting nearly 5% of pregnant women.It is a systemic disease with multiorgan involvement associated withoedema and proteinuria.It is also estimated that 25% of pregnant women with history of hypertension will develop preeclampsia during pregnancy.[10] Preeclampsia in pregnancy is the common leading cause of fetal and maternal mortality worldwide.[1]

Out of total 120 subjects participated in the study, 60 were clinically diagnosed preeclampsia patients and sixty were normotensive primigravida women.Though, there is increase in mean age of preeclampsia patients in comparison to healthy pregnant control subjects, the numerical difference was minimal and was not corresponding to established risk factor like advanced maternal age of more than 40 yrs.[11] The systolic and diastolic bloodpressure values were raised in preeclampsia subjects as expected. This is also one of the requirement for diagnosing preeclampsia.[7]

Adenosine deaminase (ADA) enzyme is distributed in lymphoid tissues and helps in deamination of adenosine and deoxyadenosine to inosine and deoxyinosine.[12] ADA is also considered to be an indicator for non-specific marker of T-cell activation.[5] In this study, mean ADA values are increased in preeclampsia patients in comparison to normotensive pregnant women and the difference is statistically significant. These results are similar to Yoneyama Yet al, Krishna M et al, and Rukmini MS et al who observed significantly higher ADA levels in preeclampsia in comparison to normal pregnancy. These results indicate that higher total ADA activity suggests increased cell mediated immunity during preeclampsia.[12–14]

A study done by Ashias J and Anuradha J showed that total serum ADA levels were higher in hyperemesis gravidarum and preeclampsia in pregnancy.[15] Also, the results of a research by Oladipo O et al demonstrated that mean ADA levels in serum of hypertensive and preeclamptic women were increased significantly than normal pregnant women. These findings suggest increased cell mediated immunity and endothelial dysfunction in preeclampsia and decreased cellular immunity in normal pregnancy.[16]

Another study conducted by Vanessa S Giorgiet al found that serum ADA levels were increased in preeclampsia group compared with normotensive and non pregnant women groups. There was a positive correlation between serum ADA and uric acid levels in women with preeclampsia. Intracellular NF-κB levels and endogenous production of IL-1β and TNF-α were increased in preeclamptic pregnant women than normotensive and non pregnant women.[17] In a prospective observational study, Shireesha V et al observed that levels of serum adenosine deaminase were elevated in eclampsia and preeclampsia patients than normotensive pregnant women.[18]

C reactive protein is a marker for acute inflammation, infection and tissue injury and is produced by hepatocytes. C-reactive protein has special importance for preeclampsia due to its relation with cytokines which are responsible for inflammatory response.[19] Cytokines act on their hepatic receptors and activate kinases and phosphatases. This in turn leads to translocation of various transcription factors on the CRP gene promoter and produce CRP.[20]

In our study, the mean serum CRP levels are significantly increased in preeclamptic pregnant women than normal pregnant women. These results are in accordance with the studies done by Nnodim Johnkennedy et al who reported that the levels of serum C–reactive protein in preeclamptic patients were significantly higher in comparison to controls.This could probably link to a response to inflammatory condition. This inflammatory condition is responsible for the release of interleukin-6 and other cytokines that enhance the synthesis of C-reactive protein by the liver.[20,21]

Some studies done by Ustun Y et al and Ghazavi et al found elevated serum levels of CRP in preeclamptic women correlated with severity of disease.[22,23] A cross-sectional study conducted by Mirzaie F et al found significantly positive correlations between serum CRP levels and diastolic blood pressure.[24] Data of the study done by Nanda K et al suggested that women having high CRP levels in first trimester would later develop preeclampsia.[7] A prospective study done by Kameswaramma K et al found that serum levels of CRP were significantly higher in patients with preeclampsia. This study also suggested that estimation of serum CRP levels in early pregnancy

may clarify the temporal relationship with severity of preeclampsia developed later.[25] A study conducted by Sacks and co-workers demonstrated that increase in CRP levels in early pregnancy can be observed as early as 4 weeks suggesting that the inflammatory response is established during the early phase of implantation.[26] Also found significantlyhigher serum CRP levels in patients of preeclampsiathan normotensive pregnant women.[21] The results of this study are consistent with this research work.

4.1. Limitation(s

Though there is high significance between the quantitative values of CRP and ADA in cases and controls, the standard deviation is also high. Sample size is small. So establishment of normal range might be difficult unless studies are done on a large population.

5. Conclusions

Serum ADA levels were significantly increased in patients of preeclampsia as compared to normotensive pregnant women, thus suggesting the role of decreased cellular immunity in normal pregnancy and increased cellmediated immunity in preeclampsia.Serum CRP levels were significantly high in preeclamptic patients thus suggesting the role of systemic inflammation and vascular endothelial cell dysfunction.Thus, it can be concluded that serum ADA and CRP could be considered as a supportive diagnostic tool in preeclampsia along with conventional markers. These levels may be helpful to predict severity of disease. Also, early detection may reduce complications and deaths due to preeclampsia in pregnancy.

6. Conflicts of Interest

No conflict of interest.

7. Source of Funding

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