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Study of Serum Concentration of CA125 in Normal and Pre-Eclampsia Patients

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Abstract: ***Objective: In this study, we wanted to evaluate the serum concentration of CA125 in pregnancies complicated by pre - eclampsia and normal pregnancies. Methods: This was a hospital based prospective observational study conducted among 120 pregnant women who came for antenatal check - up to the Department of Obstetrics & Gynaecology, JSS Hospital, Mysore, over a period of 18 months, from January 2021 to June 2022, after obtaining clearance from Institutional Ethics Committee, and written informed consent from the study participants. Results: Women with preeclampsia were primarily in the age range of 26 to 30 years, while women without preeclampsia were in the age group of 21 - 35 years.42 (70.0 %) women with preeclampsia and 32 (53.3 %) women without preeclampsia were preterm. The median CA125 among women with preeclampsia was 19 units/mL (17 - 28) and 10 units/mL (8 - 13) among those without preeclampsia. It was found that the difference was statistically significant. Conclusion: CA125 was found to be significantly elevated in preeclampsia group compared to normotensive group. Preeclampsia is linked to elevated maternal serum CA125 levels. Preeclampsia can be screened by using the biochemical marker CA125. Even though CA125 was increased in PE with severe features, it was not found to be associated with severity of the disease.***

Keywords: CA125, Preeclampsia

1. Introduction

Hypertensive disorders of pregnancy are considered to be the most significant and intriguing unsolved problems in obstetrics. The most dangerous of the hypertensive disorders are the preeclampsia syndrome, preeclampsia superimposed on chronic hypertension.5 – 10 % of all pregnancies are affected by preeclampsia and it is the leading cause of maternal morbidity, mortality and foetal morbidity and mortality worldwide. [1] Worldwide, one of the leading cause for maternal mortality is hypertensive diseases in pregnancy. [1] It is estimated by World Health Organization that percentage of maternal deaths due to hypertensive disorders is 16 % and the number of deaths each year globally due to preeclampsia is over 100, 000 with higher occurrence rate in developing countries (2.8 %) compared to developed countries (0.4 %) with prevalence in maternal and foetal morbidity ranging from 1.8 % to 16.7 %. [1, 2] In addition, it advocates to a higher incidence of cardiovascular disease later in life. Pre - eclampsia is described by ISSHP as "systolic blood pressure at ≥ 140 mm Hg and/or diastolic blood pressure at ≥ 90 mm Hg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation 1. Proteinuria (i. e. ≥ 30 mg/mol protein: creatinine ratio; ≥ 300 mg/24 hour; or ≥ 2 + dipstick); 2. Evidence of other maternal organ dysfunction, including: acute kidney injury (creatinine ≥ 90 µmol/L; 1 mg/dL); liver involvement (elevated transaminases, e. g. alanine aminotransferase or aspartate aminotransferase > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complications (e. g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); or haematological complications (thrombocytopenia – platelet count < 150000/µL, disseminated intravascular coagulation, haemolysis); or 3. Uteroplacental dysfunction (such as foetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth) ". [1]

The sources for CA125 in pregnancy are decidual cells which are influenced by inefficient trophoblastic invasion and placental separation. CA125 level increases in preeclampsia due to destruction of decidua and from severance of trophoblasts from the decidua. Various studies have supported this theory and they contend that rising levels of CA125 are a sign of the disease's escalating severity. Given that the majority of clinical investigations supporting its usage are still largely exploratory in nature, obstetrics role of CA125 has not yet been recognised. CA125 is a high molecular weight (110kD to more than 2000kD) heterogeneously structured glycoprotein. [3] Most frequently used biomarker in ovarian cancer detection is CA125 or Mucin 16, it possesses a single transmembrane domain. It has been used widely for diagnosis, follow up, treatment and recurrence of epithelial ovarian cancer. [4] Predictive biomarkers for preeclampsia have recently attracted more attention. An effective predictive test would enable early diagnosis, focused surveillance, and quick care delivery. [5] Preterm birth can be avoided with the help of a biomarker that can identify high–risk women. The PHOENIX study provides evidence of the advantages of identifying patients who are more likely to develop preeclampsia in late pregnancy. [6] Women who are in danger of acquiring a disease or by virtue of having one should be able to be identified by a reliable biomarker, allowing for risk stratification for ongoing care. An attentively planned delivery and close clinical supervision may be beneficial for these women. There are several recommendations for dividing hazards based on maternal features and pregnancy - related factors. The NICE and ACOG guidelines are frequently used examples. These guidelines perform poorly in terms of sensitivity but are straightforward, cost - free, and applicable to all expectant mothers. For instance, according to NICE recommendations, only 41 % of pregnant women with preeclampsia will show a positive screening result. [7] There are two screening tests which are available during the past ten years have been utilized in some clinical settings as part of care. The first is a screening test conducted in the first trimester that identifies people who are susceptible to preterm preeclampsia. The second is intended for use in later stages of pregnancy when it is clinically unknown if preeclampsia is present or likely to develop. To address this, a new early

trimester screening method has been developed, and it has been verified using the levels of PlGF. In comparison to just clinical risk factors, this test is up to 82 % more accurate at predicting preterm preeclampsia, [8] the test's implementation costs, though, are a problem and a restriction. Another biomarker innovation, to be used throughout the third trimester, has entered the clinic in addition to the combination screening algorithm for the first trimester. Preeclampsia causes a considerable derangement in the anti - and proangiogenic factors like sFlt - 1 and PlGF. [9] 38 or less of sFlt/PlGF ratio can successfully rule out the chance of preeclampsia for the remainder of the week. In some centres, it has been used in clinical practice as a result. PlGF by itself has also been tested as a means of prioritizing care for pregnant women who may have preeclampsia. The cost element is a big limitation, despite the tremendous advancements made over the previous decade with the advent of these new biomarker tests. So, the interest is shifting towards identifying a biomarker which is economical, reliable, and universally applicable. One such marker which appears to be promising is CA125. Although there are other good screening tests with biomarkers such as platelet derived growth factor, beta hCG, PAPP - A, sFLT - 1/placental growth factor (PGF) ratio; these are not appropriate for straightforward, inexpensive, and quick routine clinical examinations due to logistical and financial considerations. Most of them require well equipped laboratories.

In this study we wanted to evaluate the levels of serum concentration of CA125 in normal and preeclampsia pregnancies along with the relationship between CA125 and severity of preeclampsia.

2. Materials and Methods

This was a hospital based prospective observational study conducted among 120 pregnant women who came for antenatal check - up to the Department of Obstetrics & Gynaecology, JSS Hospital, Mysore, over a period of 18 months, from January 2021 to June 2022, after obtaining clearance from Institutional Ethics Committee, and written informed consent from the study participants.

Inclusion Criteria

1) Singleton pregnancies
2) Period of gestation: Between 20 to 40 weeks
3) Maternal age: 18 - 35 years

Exclusion Criteria

1) Pregnant women with chronic hypertension, renal disease, cardiovascular disease or autoimmune disease
2) Pregnant women with irregular ANC follow – up

Socio demographic and clinical details were obtained from pregnant women/study subjects. A general, physical and obstetric examination was carried out.3 ml of venous blood sample was collected which was centrifuged within 2 hours and serum CA125 was measured using CLIA method.

Study Procedure

120 expectant women who met the inclusion and exclusion requirements were studied. Informed and written consent was obtained from the patients. History, general physical, systemic and obstetric examination was done. Under aseptic conditions, 3 mL of venous blood was collected in a plain vacutainer and the sample was sent to biochemistry department. Sample was centrifuged within 2 hours. CA 125 was measured using CLIA method. CA125 values obtained was compared between normal and preeclampsia patients.

Statistical Analysis

Data was entered into an excel spreadsheet, and descriptive statistics such as mean, median, standard deviation, frequency, and percentage was computed. The statistical analysis was carried out using SPSS (Statistical Package for Social Sciences) version 20 (IBM SPASS statistics [IBM corp. released 2011]).

3. Results

Table 1: Participants Age Distribution in the Study

Age Group	Pre - eclampsia		Total
	Present	Absent	
< 20	39 (5.0)	5 (8.3)	8 (6.7)
21 - 25	18 (30.0)	29 (48.3)	47 (39.2)
26 - 30	20 (33.3)	15 (25.0)	35 (29.2)
31 - 35	17 (28.3)	10 (16.7)	27 (22.5)
36 - 40	2 (3.3)	1 (1.7)	3 (2.5)
Total	60	60	120

Preeclamptic women were primarily in the age range of 26 to 30 years, while non - preeclamptic women were in the range of 21 to 35 years.

Table 2

Period of Gestation	**Pre - eclampsia**		**Total**	**X^2**	**P**
	Present	**Absent**			
Pre term	42 (70.0)	32 (53.3)	74 (61.7)	4.357[a]	0.037
Term	18 (30.0)	28 (46.7)	46 (38.3)		
Total	60	60	120		
Distribution of Research Participants according to Gestational Period					
Gravida	**Pre - eclampsia**		**Total**	**X^2**	**P**
	Present	**Absent**			
Primi	34 (56.7)	30 (50.0)	64 (53.3)	1.256	0.739
Gravida 2	13 (21.7)	18 (30.0)	31 (25.8)		
Gravida 3	10 (16.7)	10 (16.7)	20 (16.7)		
Gravida 4	3 (5.0)	2 (3.3)	5 (4.2)		
Total	60	60	120		
Distribution of Research Participants according to Gravida Score					

It can be observed that 42 (70.0 %) women with preeclampsia and 32 (53.3 %) without preeclampsia were preterm. Preeclampsia and gestational age were associated statistically.

About 34 (56.7 %) of women with pre - eclampsia and 30 (50.0 %) without pre - eclampsia were primigravida.

Pre - eclampsia	Mean	Std. Deviation	t	P
Present	34.47	3.96	1.798	0.075
Absent	35.77	3.95		
Comparing the Average Gestational Age of Pregnant Women with and Without Pre - eclampsia				
Pre - eclampsia	**Mean**	**Std. Deviation**	**t**	**P**
Present	158.63	15.99	18.291	0.001
Absent	116.27	8.13		
Comparison of Mean Systolic Blood Pressure Among Women with and Without Pre - eclampsia				
Table 3				

The mean period of gestation among women with pre - eclampsia was 34.47 ± 3.96 weeks and 35.77 ± 3.95 weeks among those without pre - eclampsia. The statistical significance of this discrepancy was not established.

Pre - eclampsia	Mean	Std. Deviation	t	P
Present	102.87	9.97	17.412	0.001
Absent	77.87	4.92		
Comparison of Mean Diastolic Blood Pressure Among Women With and Without Pre - eclampsia				
Pre - eclampsia	**Median**	**IQR**	**Z**	**P**
Present	19	17 - 28	8.423	0.001
Absent	10	8 - 13		
Comparison of Median CA 125 Levels Among Women With and Without Pre - eclampsia				
Severity	**Median**	**IQR**	**Z**	**P**
With severe features	19.5	16 - 27	0.060	0.952
Without severe features	18.5	17 - 29		
Comparison of Median CA 125 Levels Among Women With and Without Severe Pre - eclampsia				
Table 4				

The mean systolic blood pressure among women with pre - eclampsia was 158.63 ± 15.99 mmHg and 116.27 ± 8.13 mmHg among those without pre - eclampsia. It was determined that this difference correlated statistically.

The mean diastolic blood pressure among women with pre - eclampsia was 102.87 ± 9.97 mmHg and 77.87 ± 4.92 mmHg among those without pre - eclampsia. A statistically significant difference was discovered between these two.

The median CA 125 among women with pre - eclampsia was 19 (17 - 28) and 10 (8 - 13) among those without preeclampsia. It was determined that this difference was associated statistically.

The median CA 125 among women with severe pre - eclampsia was higher than those without severe preeclampsia. It was determined that there was no correlation statistically between the study subjects.

4. Discussion

Preeclampsia is a hypertensive pregnancy disease that puts both the mother and the unborn child at risk for morbidity and even death. The most obvious symptom of preeclampsia is elevated blood pressure, and this condition can be harmful to the liver, kidneys, and whole endothelium of the mother by generating vasoconstrictive substances. [1] Initially discovered on the exterior of the OVCA433 ovarian cancer cell line was a 200 - kDa glycoprotein antigen known as CA - 125. [2] CA - 125 is abundantly found on the surface of both healthy and cancer cells of mesothelial origin, as well as the normal vaginal canal, amniotic membranes, pleural surface, pericardial surface, peritoneal surface, and endometrial cells. Serum CA - 125 levels are seen in foetal chorion and decidua, more seen during the early trimester of pregnancy and the postpartum period. [2]

Although various hypotheses have been put forth in an effort to explain how preeclampsia develops, its precise pathophysiology is still unknown. Currently, it is believed that the illness has two stages. The 1st stage's significant variability places the placenta at risk for hypoxia, which boosts cytokine production. The cytokines produced causes endothelial cell damage, changes in vascular response, reduced intravascular volume, inflammation, and the well–known lesion of glomerular endotheliosis during the 2nd stage. The maternal vulnerability to the changes, on the other hand, is a significant underlying component. Due to the absence of developed immunological tolerance during pregnancy, the placenta and foetus's paternal antigens may be the target of an immune reaction. As a result, the process of placentation is stopped, and cytotrophoblast invasion is reduced. Following this, the placenta experiences hypoxia and starts to release inflammatory mediators that affect the vascular endothelium. [10, 11]

High serum CA125 levels, which are found throughout the early trimester of pregnancy and following childbirth, have been linked to the foetal chorion, maternal decidua, as well as amniotic fluid. Decidual damage and dissociation of trophoblasts are considered to be the mechanism causing the rise in CA125. [12]

Pregnancies complicated by preeclampsia can benefit from the same process. Due to inadequate invasion of trophoblasts, there is activation of process of inflammation throughout the placenta, are thought to be potential causes of CA - 125 expression. Several clinical studies have been done to determine whether or not this increase in CA - 125 expression will manifest biochemically and clinically or not. [2, 13]

As far as we know, Schrocksnadel et al. [14] had made the initial comparisons of CA125 levels in healthy pregnant women (singleton and term), pregnant patients with hypertensive problems, and healthy women (non - pregnant).

There was no statistically significant difference or upward trend. This discovery was later supported by a long term–controlled investigation that examined the CA125 levels of preeclamptic and healthy participants over a predetermined period of time. According to the findings of this investigation, there was no relationship between gestational age and the serum levels of CA125. For pregnancies that are likely to result in preeclampsia, there was a tendency toward an increase in CA125 concentrations. [15] Another investigation compared the serum CA125 of 350 women with a normal pregnancy outcome to those of 120 women with pathological pregnancy outcomes, including spontaneous abortions, intrauterine foetal death, IUGR, congenital and structural anomalies, and preeclampsia/eclampsia. It was noted that maternal CA125 blood levels were not statistically different from those found in pathological pregnancies although compared to the second trimester, were much higher in the 1st and 3rd trimesters of pregnancy.

56 healthy pregnant women and 54 preeclamptic/eclamptic women were the subjects of a study by Cebesoy et al. [13] Pregnant women without preeclampsia or eclampsia were shown to have considerably lower blood levels of CRP and CA125 than pregnant women without these conditions. Additionally, women with severe preeclampsia/eclampsia had considerably greater serum levels of CRP and CA125 than those with mild preeclampsia. Significant associations between albumin, CRP, CA - 125, and MAP were also discovered. The scientists came to the conclusion that preeclampsia is characterized by elevated levels of CRP and CA125.

In the current research, most of the women with preeclampsia were in the age group of 26 to 30 years and without preeclampsia were in the age group of 21 to 35 years. We found that 42 (70.0 %) of women with preeclampsia and 32 (53.3 %) without preeclampsia were preterm. Preeclampsia and gestational age were statistically correlated with one another.

In the study of the demographic data of the patients enrolled, the two study groups control and preeclamptic groups showed no statistically significant difference regarding the maternal age but there was differences that was statistically significant regarding the mean of gestational age. In a similar study by Osanyin et al. age of the mother and gestational age of the individuals at enrolment did not differ significantly. [16]

The mean period of gestation among women with preeclampsia was 34.47 ± 3.96 weeks and 35.77 ± 3.95 weeks among those without preeclampsia. In the current study it was not determined that this difference was statistically significant. ($p = 0.075$).
Within this research, the mean systolic blood pressure among women with preeclampsia was 158.63 ± 15.99 mmHg and 116.27 ± 8.13 mmHg among those without preeclampsia, the statistical significance of this discrepancy was discovered. ($p = 0.001$). The mean diastolic blood pressure among women with preeclampsia was 102.87 ± 9.97 mmHg and 77.87 ± 4.92 mmHg among those without preeclampsia, hence statistically significant ($p = 0.001$) difference was found. These results agree with the study of Said et al. which revealed that the systolic and diastolic blood pressure were statistically significant between control and studied groups ($p = 0.001$). [5]

Osanyin et al. discovered that in their clinical and laboratory data, there were statistically significant disparities., including serum CA125 levels, proteinuria, platelet count, serum creatinine, and serum uric acid ($p = 0.001$, $p = 0.005$, $p = 0.012$, $p = 0.005$, and $p = 0.001$, respectively). [16]

In the present study, the median CA125 among women with preeclampsia was 19 units/mL (17 - 28) and 10 units/mL (8 - 13) among those without preeclampsia. This showed statistically significant ($p = 0.001$) disparities. Those with severe preeclampsia had a higher median CA125 than women without severe preeclampsia. Even though CA125 median values were higher this difference was not determined to be statistically significant ($p = 0.952$). In Ozat et al. study, 50 mIU/L was the detection threshold for their patients; [17] Threshold of 47.4 mIU/L was employed in the Osanyin et al. investigation; in the Gottipatti et al. trial, the mean value of CA125 in the preeclampsia group was 56.6 IU/mL. [16] Our Sn and Sp values were 70.1 % and 62.0 %, respectively, when ROC curve was used with the above detection threshold to determine whether maternal blood CA125 levels and preeclampsia are related. [16]

Additionally, according to Bon et al. preeclampsia was unrelated to higher maternal blood levels of CA125 during the early and late trimester of pregnancy [18] but in de Groot et al. study, researchers tracked the CA125 levels of pregnant women (both non hypertensives and those who went on to develop preeclampsia) over a period. They discovered that CA125 levels were unaffected by gestational age or the outcome of the pregnancy, but they suggested a pattern indicating an increase in CA125 concentrations for pregnancies that are probably to result in preeclampsia. The serum concentrations of CA125 were significantly higher in the present study as well as the results published by Cebesoy et al. in women with preeclampsia. [13] They suggested that ascites, which is seen in preeclamptic women and results from hypoalbuminemia, is likely what causes the rise of CA125 in preeclampsia. [13] According to a proposal by Karaman et al. [2] trophoblastic invasion failure coupled with the stimulation of an inflammatory process inside the placenta causes the production of CA125 in preeclampsia, this idea was supported by Ozat et al. [17] Additionally, Osanyin et al. discovered that women with preeclampsia had CA125 serum levels that are considerably higher. Most of the research, including the current study, found that mean CA125 readings were higher in the preeclampsia group, supporting the theory that increasing disease severity causes an increase in inflammatory response, which causes an increase in CA125 release. It is possible to speculate that preeclampsia possibly causes the secretion of CA125 within the placenta due to the expansion of decidual damage and inadequate trophoblastic invasion. [16]

Said et al. found similar results in their study where the mean serum concentration of CA125 was found to be high in severe preeclampsia group compared to control group which indicates that serum CA125 level increases with the severity of preeclampsia. [5] This could be explained by a blood CA125 level linked to defective placentation, which results in

periodic disruption of placental perfusion, ischemia - reperfusion type injury, free oxygen radical stress, and systemic inflammatory response. This was also in agreement with the study by Karaman et al. who found that the increased mean serum CA125 could be secondary to underlying inflammatory process which may play a role with the severity of preeclampsia in patients. [2] Maternal decidua, foetal chorion, amniotic fluid, and the period following childbirth are all possible causes of this rise. The development of ascites as a result of the decreased albumin level is another potential explanation for the rise of maternal serum CA125 in females with severe preeclampsia. Females with severe preeclampsia had significantly lower albumin levels than those with mild preeclampsia and healthy pregnancies. Increased CA125 levels and peritoneal discomfort could result from ascites. [2]

Karumanchi and Naljayan documented an association between increased uric acid levels and the disease severity. Manya et al. stated that serum uric acid levels in preeclampsia may have increased due to reduced renal tubular excretion. More recently, it has been suggested that the generation of reactive oxygen species under oxidative stress are additional source of the hyperuricemia seen in preeclampsia.

Osanyin et al. study, indicated a favourable correlation with statistical significance between maternal serum CA125 and several clinical and laboratory indicators of disease severity, including SBP and DBP, urinary protein levels, platelet count, and serum uric acid. [16] Increased blood pressure (both systolic and diastolic), proteinuria, platelet counts, serum creatinine, and serum uric acid all have diagnostic and predictive roles in preeclampsia, which the study confirmed. [19 - 21]

It is clear that the study's evaluated population has to be significantly smaller for the correct determination of a specific CA125 value that would specifically identify pregnant women at risk for preeclampsia. The size of the study sample, variations in the demographic and clinical characteristics of the patients under review, and the use of various diagnostic criteria for hypertensive disorders of pregnancy may all be contributing factors to the discrepancies between current findings and those of the earlier studies. The variability in the precision and dependability of CA125 assays may also be a confusing factor.

According to this study, preeclamptic pregnancy has higher serum CA125 levels than normotensive pregnancy. Even though the level of CA125 was higher among preeclampsia with severe features, it did not correlate statistically when compared to those without severe features. The study stresses that CA125 may serve as a biomarker for preeclampsia. The relationship between CA125 levels and the severity of preeclampsia needs to be further investigated.

In conclusion, CA125 was found to be significantly elevated in preeclampsia group compared to normotensive group. The results of this study suggest that preeclampsia is linked to elevated maternal serum CA125 levels. Preeclampsia can be screened by using the biochemical marker CA125. Even though CA125 was increased in PE with severe features, it was not found to be associated with severity of the disease Additional research is required to assess the use of increasing serial CA125 levels as a disease severity marker.

Disclosure Statement

All authors report no conflict of interest

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