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Alterations in Serum Protein Profile in Preeclampsia: A Comparative Study with Normotensive Pregnancy and Its Relation to Disease Severity and Parity

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ABSTRACT

***Background*:** Preeclampsia (PE) is a multisystem disorder of unknown etiology. It is a common cause of both maternal and perinatal morbidity and mortality in both developed and developing countries. Preeclampsia is a pregnancy-specific multisystem disorder characterized by hypertension, proteinuria, and widespread endothelial dysfunction. Alterations in maternal serum protein profile, particularly serum albumin and albumin-to-globulin (A:G) ratio, may reflect disease severity and underlying pathophysiological changes. However, data regarding their association with severity and parity of preeclampsia remain limited. It is believed that the pathophysiological changes occurring in preeclampsia may result from the abnormal expression of some proteins.

***Aim &objective*:** The objective behind the study was to determine the serum Total Protein, Albumin & A:G ratio in normotensive & preeclamptic (mild & severe) pregnant women, & to correlate, if any, relation with severity and parity of preeclampsia.

Material & method: The study was carried out in the Department of Biochemistry with collaboration with Department of Obstetrics and Gynaecology at Gauhati Medical College & Hospital, Guwahati, in a group of 90 pregnant women who were subdivided into three groups-30 women with severe preeclampsia,30 with mild preeclampsia &30 gestational period & age matched normotensive pregnant as control.

Results & observation: The mean serum Total Protein level was very significantly low in severe PE (mean± SD=5.68± 0.366) and in mild PE (6.24± 0.53), in comparison to normotensive pregnancy (6.60±0.49); p-value <0.001. Albumin decreased to 3.35± 0.41 in normotensive pregnancy to 3.02±0.30 in mild PE & to 2.11±0.29 in severe PE, was highly significant (p<0.001). The A:G ratio also decreased very significantly from 1.04±0.16 in normotensive to 0.97±0.17 in mild & 0.65±0.12 in severe PE (p<0.001). There was no significant change in levels of Total Protein, Albumin, Globulin and A:G ratio in relation to parity in all three groups respectively.

Conclusion: It was concluded from our study that Total Protein, Albumin & A:G ratio was found to be decreased, while no significant change in Globulin with mild & severe preeclampsia as compared to normotensive pregnancy and not influenced by parity.

Keywords: *Preeclampsia, Total Protein, A:G ratio, Pregnancy, Parity.*

INTRODUCTION

Pregnancy is a very special time in a woman's life and becoming a mother is a precious gift of God to every woman. In normal pregnancy, presence of rapidly developing and apparently well tolerated allografts i.e. the fetus with numerous metabolic alterations are seen. These changes are expected to produce alterations in serum protein pattern of mother. Preeclampsia (PE) is a pregnancy-specific syndrome that can affect virtually every organ system. Preeclampsia /eclampsia are one of the commonest causes of high maternal and infant mortality and morbidity rates.[1] It is a multisystem disorder of unknown etiology characterised by development of hypertension to the extent of 140/90 mm Hg or more with proteinuria (≥300mg/day) after the 20th week in a previously normotensive and non-proteinuric patient. It has been estimated that worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders.[3]. A review article conducted between 2000-2010 found worldwide, the incidence of preeclampsia ranges between 2% and 10% of pregnancies. WHO estimates the incidence of preeclampsia to be seven times higher in developing countries than in developed countries.[4] In India, several studies have emphasized that the incidence of pre-eclampsia in our country is greater than that in the developed countries. However, there is only limited data on the actual incidence and maternal mortality due to the disease.

Pre-eclampsia can be potentially dangerous for both mother and the fetus. Preeclampsia is still regarded as "a disease of theories" and its etiology has remained poorly understood (Dekker G et al. 1998).[5] Although the specific cause of preeclampsia remain unknown, endothelial dysfunction has been considered as central in the pathophysiology of it (Roberts J et al.1989).[6] This endothelial dysfunction may further be worsened by several vasoactive markers that are elevated in pre-eclampsia, such as cellular fibronectin, endothelin, platelet-derived growth factor, soluble E-selectin, soluble tissue factor, and Von Willebrand factor. It is generally believed that the pathophysiological changes occurring in preeclampsia may result from the abnormal expression of some proteins. Many investigations studying a single or several proteins have detected concentrations in pregnancy which varies significantly from expected average values observed in non-pregnant female (Mack, 1960). Liu et al.2011 identified Fifty-one proteins that are differentially expressed between severe PE women and healthy pregnant women.[8]

Albumin was found to be lower in women with severe PE (Benoit & Rey, 2011).[9] When PE is accompanied by proteinuria there is a remarkable fall in albumin and an increase in alpha (2) macroglobulin level (Horne *et al.,* 1970).[10] Studies have shown that the expression levels of these proteins are increased or decreased according to the disorder and its degree in PE.

Tandon *et al.,* (1985) [11] revealed significant rise in mean levels of serum α 1, α 2 and *B*- globulin in pregnant women as compared to non-pregnant controls. The rise may be due to increase in pregnancy associated proteins

OBJECTIVES

1. To compare serum protein ratio in normotensive pregnancy and pregnancy with preeclampsia in gestational period & age matched cases.
2. To correlate, if there exists any correlation between serum levels and ratio with severity and parity of preeclamptic cases.

MATERIALS AND METHODS

This case control study was conducted in the Department of Biochemistry with collaboration with Department of Obstetrics and Gynaecology, Gauhati Medical College & Hospital, Guwahati, between the periods from August, 2021 to July, 2022.

The study was conducted in three broad groups between 18-35 years of age with gestational age 20-40 weeks.

Group I (Control group) comprised of 30 apparently healthy normotensive pregnant women. Group II comprised of 30 Mild preeclamptic women: BP ≥ 140/90 mm Hg but <160/110 mm of Hg without significant proteinuria. On Dip stick:1+. Group III comprised of 30 Severe Pre-eclamptic BP ≥160/110 mm of Hg with significant proteinuria Dip stick ≥3+. Pregnant women with pre-existing hypertension, Diabetes Mellitus, Chronic Liver disease, Multiple pregnancies, Chronic Renal disease, Cardiovascular Disease were excluded from the study. The written inform consent was taken from all the cases and controls prior to include in study.

5 ml venous blood from antecubital vein was collected. The blood was allowed to clot. Serum was obtained by centrifugation and 2 ml of serum was frozen at -80^0 C till estimation.

SERUM TOTAL PROTEINS WAS ESTIMATED BY BIURET METHOD.[12]

Principle - Proteins, in an alkaline medium, bind with the cupric ions present in the biuret reagent to form a blue-violet coloured complex. The intensity of the colour formed is directly proportional to the amount of Proteins present in the sample.

Proteins + Cu^{++} ⟶ Blue Violet Coloured Complex

SERUM ALBUMIN WAS ESTIMATED BY BROMOCRESOL GREEN (BCG) MRTHOD.[13]
Principle- albumin binds to bromocresol green in a buffered medium to form a green coloured albumin – BCG complex. The Intensity of colour formed is directly proportional to albumin concentration in sample.

Albumin + bromocresol green → Albumin BCG Green complex

A dipstick urine measurement for protein was performed on a random urine sample using multistix reagent strips (Bayer).

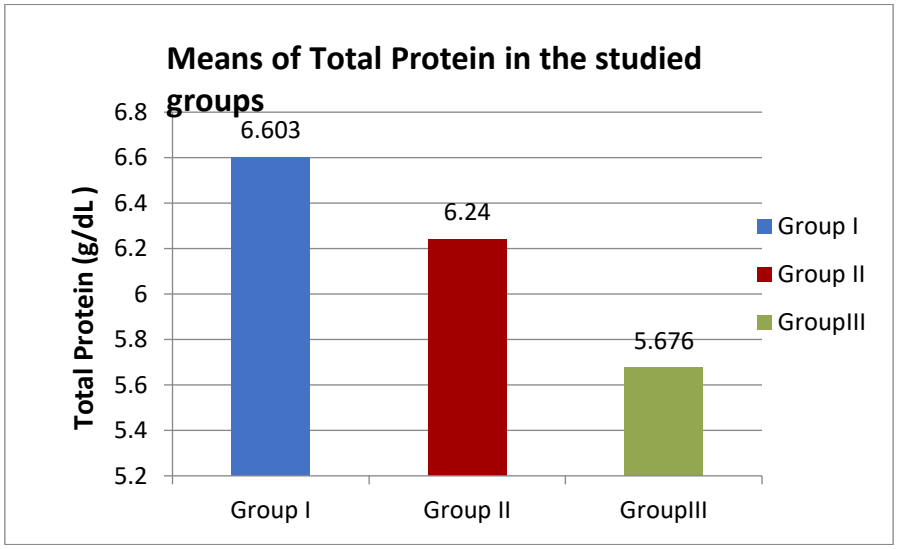
Statistical Analysis:
Descriptive data was represented as mean and standard deviation. One way Analysis of variance (ANOVA) was used to compare biochemical parameters between the cases and controls. Correlations were observed by using Pearson's correlation coefficient. The results were considered significant when the probability (p-value) was less than 0.05 of the observed values of "t" at a particular degree of freedom.

RESULTS
Table 1 represents comparison of biochemical parameters among the study groups. The means of serum Total Protein in the three groups were 6.60 g/dL, 6.24g/dL and 5.68 g/dL respectively, and the comparison of means among the study groups were very significant (<0.001). The means of serum Albumin in the three groups were 3.35 g/dL, 3.02 g/dL and 2.11 g/dL respectively and the difference between the three groups were very significant (<0.001). The mean values of Globulin did not show any statistical difference among the study groups (>0.05). The A:G ratio also decreased very significantly from 1.04±0.16 in normotensive to 0.97±0.17 in mild & to 0.65±0.12 in severe PE (p <0.001).

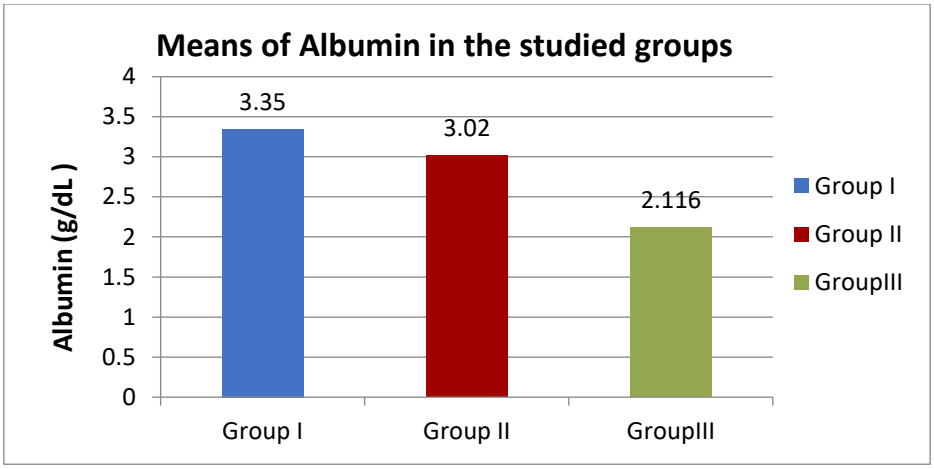
Table 1: Comparison of Biochemical Parameters among study group

Parameters	Group I (Mean± SD)	Group II (Mean± SD)	Group III (Mean± SD)	p- value
Total Protein(g/dL)	6.60±0.49	6.24±0.53	5.68±0.37	<0.001
Albumin(g/dL)	3.35±0.41	3.02±0.30	2.11±0.29	<0.001
Globulin(g/dL)	3.25±0.28	3.22±0.46	3.37±0.22	0.20[NS]
A:G ratio	1.04±0.16	0.97±0.17	0.65±0.12	<0.001

*very significant (<0.001)), [NS] Not significant



Graph: Showing comparison of Serum Total Protein means in the studied groups.



Graph: Showing comparison of Serum Albumin means in the studied groups.

Table: 2,3 4 shows that subjects were then divided into two groups according to parity. There was no significant change (p>0.05) in the level of Total Proteins, Albumin and A:G ratio in two parity groups.

Table 2: Showing comparison of Serum Total Protein in the studied groups in relation to Parity.

Total Protein(g/dL)	Primiparous	Multiparous	p- value
Group I	6.72±0.43	6.5±0.50	0.31^{NS}
Group II	6.20±0.44	6.27±O.61	0.62^{NS}
Group III	5.70±0.37	5.6±0.29	0.54^{NS}

^{NS} –non significant

Table3: Showing comparison of Serum Albumin in the studied groups in relation to Parity.

SerumAlbumin (g/dl)	Primiparous	Multiparous	p- value
Group I	3.43±0.39	3.38±0.41	0.75^{NS}
Group II	3.01±0.29	3.05±0.35	0.73^{NS}
Group III	2.30±0.32	2.19±0.28	0.32^{NS}

^{NS} –non significant

Table 4: Showing comparison of A:G ratio in the studied groups in relation to Parity

A:G ratio	Primiparous	Multiparous	p- value
Group I	1.039±0.17	1.038±0.15	0.62^{NS}
Group II	0.926±0.17	0.967±0.20	0.55^{NS}
Group III	0.651±0.13	0.645±0.12	0.90^{NS}

^{NS} –non significant

A total of 90 pregnant women were included in the study and divided into three groups: normotensive pregnant women (Group I, n=30), women with mild preeclampsia (Group II, n=30), and women with severe preeclampsia (Group III, n=30). The mean serum total protein levels showed a statistically significant decline across the three groups, being highest in normotensive pregnant women (6.60 ± 0.49 g/dL), followed by mild preeclampsia (6.24 ± 0.53 g/dL), and lowest in severe preeclampsia (5.68 ± 0.37 g/dL), with the difference among groups being highly significant ($p < 0.001$). Similarly, mean serum albumin levels were significantly reduced in preeclamptic women compared to controls, decreasing progressively from 3.35 ± 0.41 g/dL in normotensive pregnancies to 3.02 ± 0.30 g/dL in mild preeclampsia and 2.11 ± 0.29 g/dL in severe preeclampsia ($p < 0.001$).

In contrast, mean serum globulin levels did not show any statistically significant difference among the three groups (3.25 ± 0.28 g/dL in Group I, 3.22 ± 0.46 g/dL in Group II, and 3.37 ± 0.22 g/dL in Group III; $p > 0.05$). The albumin-to-globulin (A:G) ratio demonstrated a significant downward trend with increasing severity of preeclampsia, declining from 1.04 ± 0.16 in normotensive pregnant women to 0.97 ± 0.17 in mild preeclampsia and 0.65 ± 0.12 in severe preeclampsia, which was highly significant ($p < 0.001$).

Further analysis based on parity revealed no statistically significant difference in serum total protein, serum albumin, or A:G ratio between primiparous and multiparous women within any of the three study groups ($p > 0.05$). These findings indicate that alterations in serum protein parameters are primarily associated with the presence and severity of preeclampsia rather than parity.

DISCUSSION

Plasma albumin, the major determinant of the total colloid osmotic pressure of plasma is regarded as a biomarker for reliable risk prediction in various clinical settings. Concentration of serum albumin is influenced by various factors, including its synthetic rate, catabolic rate , extravascular distribution exogenous loss . The present study showed that serum concentration of total protein, albumin, and A:G ratio was significantly reduced in pre-eclampsia, while the change in level of globulin was not significant. The result of our finding corroborates with that of Muzammil S *et al* 2014 . The fall in protein concentration seen during pregnancy most likely is a result of hemodilution, since total protein concentration is inversely related to plasma water concentration. The decrease in levels of serum albumin during pregnancy and preeclampsia is well known (Hofmeyr *et al.,* 1991; Studd *et al.,* 1970).[14,15] The intravascular mass of albumin is unchanged in normal pregnancy and that the sustained hypoalbuminemia is due to hemodilution (Honger,1967).[16] The albumin synthesis is significantly greater in preeclampsia than in normal pregnancy, probably because of diminished production of oestrogen by foetoplacental unit or simply because the more profound hypoalbuminemia of preeclampsia is a greater stimulus to albumin synthesis by liver. This lower concentration of serum albumin is claimed to be result of proteinuria and hypercatabolism of albumin with no detectable loss of albumin in interstitial fluid .[17] On the other hand Mendenhall ,(1970) demonstrated that gestation associated with a decrease in albumin concentration with no variation in serum immunoglobulins levels. Studd and Blainey (1969) had suggested that pre-eclamptic toxemia is the most common cause of nephrotic syndrome but De Wardener (1967) did not agree that pre eclampsia fits the definition of nephrotic syndrome, because he claimed that plasma proteins are relatively normal and proteinuria is never more than 5 mg/day. Present study demonstrates that the considerable change in serum proteins that occur in pre-eclampsia can be a result of heavy proteinuria Olooto et al., found low serum albumin in preeclamptic women compared to normal pregnancies.[18] Serum albumin levels may act as an indicator of the severity of preeclampsia Gojnic *et al.*(2004).[19] If serum albumin level is below 2.5 g/dL, the risks of ascites, perinatal mortality and hemolysis elevated liver enzymes low platelet (HELLP) syndrome are increased markedly Seong *et al*.(2010).[20] Increased capillary permeability secondary to endothelial damage is explained to be partly responsible for the low plasma albumin observed in preeclampsia. Also from this study, serum total protein were found to be significantly low ($p < .001$) in preeclampsia as compared to the control group. Preeclampsia is associated with increased capillary permeability secondary to endothelial damage and this seems to be partly responsible for the observed proteinuria and consequent significant low serum total protein and albumin levels. Hypoalbuminemia in preeclampsia is thus a consequent of urinary protein loss and reduced hepatic blood flow secondary to haemoconcentration created by high filtration pressure in capillaries. Linking to the observed low serum albumin in pregnant women partly to under nutrition need not be over emphasized since the sample population is obtained from a developing nation whose citizenry are prone to under nutrition.

Preeclampsia is a complex multisystem disorder characterized by widespread endothelial dysfunction, increased vascular permeability, and proteinuria, all of which contribute to alterations in maternal serum protein profile. In the present study, serum total protein, albumin, and albumin-to-globulin (A:G) ratio were found to be significantly decreased in women with mild and severe preeclampsia compared to normotensive pregnant women, with a progressive decline corresponding to disease severity, while globulin levels remained largely unchanged.

Recent studies from 2024 and 2025 strongly support these observations. **Sethi et al. (2024)**[21] demonstrated significantly reduced serum albumin levels and elevated ischemia-modified albumin in preeclamptic women, highlighting the role of oxidative stress and endothelial injury in albumin modification and loss. Their findings suggest that albumin depletion in preeclampsia reflects both quantitative loss through proteinuria and qualitative structural alterations induced by oxidative stress.

Similarly, **Dal et al. (2024)**[22] evaluated albumin-based composite indices such as the hemoglobin-albumin-lymphocyte-platelet (HALP) score and reported significantly lower albumin values in severe preeclampsia, associating hypoalbuminemia with heightened inflammatory response and adverse maternal outcomes. These results reinforce albumin's role as an integrated marker of inflammation, nutritional status, and endothelial integrity.

In a large retrospective analysis, **Zhang et al. (2025)**[23] investigated the fibrinogen-to-albumin ratio (FAR) and demonstrated that lower albumin concentrations and higher FAR values were independently associated with increased severity of preeclampsia and poor perinatal outcomes. This study emphasized that hypoalbuminemia contributes to disease progression by reducing plasma oncotic pressure, thereby aggravating edema, hemoconcentration, and placental hypoperfusion.

Proteomic studies by **Liu and colleagues (2024)**[24] further revealed that although total globulin levels may not show significant variation, specific globulin fractions and inflammatory proteins are differentially expressed in preeclampsia. This finding explains why routine globulin estimation often appears unchanged, as observed in the present study, despite significant molecular alterations occurring at the proteomic level.

The absence of any significant association between parity and serum protein parameters in the current study is consistent with findings reported by **Kumar et al. (2024)**[25] who concluded that biochemical alterations in preeclampsia are predominantly disease-driven rather than influenced by obstetric history. This suggests that hypoalbuminemia and reduced A:G ratio can serve as universal biochemical indicators of disease severity irrespective of parity.

Overall, accumulating evidence from recent literature supports the concept that serum albumin and related protein ratios are not merely laboratory abnormalities but reflect the underlying pathophysiological processes of preeclampsia, including endothelial dysfunction, capillary leak, inflammation, and renal involvement

These observations indicated that total proteins, albumin, and A:G ratio was found to be decreased, while there was no change in levels of globulins with pre-eclampsia as compared to normal pregnancy. There was no influence of parity on serum protein levels.

CONCLUSION

In conclusion, the present study demonstrates that serum total protein, serum albumin, and albumin-to-globulin ratio are significantly reduced in preeclamptic pregnancies, with a progressive decline observed from mild to severe disease, while globulin levels remain largely unaffected. These biochemical alterations correlate strongly with the severity of preeclampsia but show no significant association with parity. Recent studies from 2024 and 2025 further validate serum albumin as a reliable marker of disease severity and emphasize its potential role in risk stratification and early identification of high-risk preeclamptic patients. Routine assessment of serum albumin and protein ratios may therefore serve as a simple, cost-effective adjunct in the clinical evaluation and monitoring of preeclampsia, particularly in resource-limited settings.

Limitations

1. **Sample size and single-centre design:** The study included 90 women from one tertiary hospital; findings may not generalize to other populations or care settings.
2. **Cross-sectional measurement:** Single time-point serum measure
    a. s. protein and preclampsia
    b. of temporal trajectories (e.g., whether albumin decline precedes clinical deterioration). Prospective serial sampling would be informative.
3. **Bulk protein measures:** Total globulins were measured as a single group; fractionated or proteomic analyses might identify specific globulin changes missed here.
4. **Potential confounders:** Nutritional status, undiagnosed chronic disease, or acute infections could influence albumin/protein levels. Although major co-morbidities were excluded, residual confounding cannot be excluded.
5. **Lack of standardized cut-offs:** There is no universally accepted albumin threshold for PE severity; heterogeneity among 2024–2025 studies means direct clinical implementation requires validation.

Declarations:
Conflicts of interest: There is not any conflict of interest associated with this study.
Consent to participate: There is consent to participate.
Consent for publication: There is consent for the publication of this paper.
Authors contributions: Authors equally contributed the work.

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