Section: Pathology

Original Research Article

COMPARATIVE ANALYSIS OF NATURAL ANTICOAGULANT PROTEINS (PROTEIN C, PROTEIN S, AND ANTITHROMBIN III) IN PREECLAMPSIA: A CASE–CONTROL STUDY FROM A TERTIARY CARE CENTRE IN NORTH INDIA

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ABSTRACT

Background: Preeclampsia is characterized by systemic endothelial dysfunction and a heightened prothrombotic milieu. Alterations in natural anticoagulant proteins – Protein C (PC), Protein S (PS), and Antithrombin III (ATIII) – may contribute to its pathogenesis. **Aim:** To compare plasma levels of PC, PS, and ATIII in preeclamptic versus normotensive pregnant women.
Materials and Methods: In this case control study conducted at Al Falah School of Medical Sciences & Research Centre, Faridabad, from January 2023 to December 2024, 50 women with preeclampsia (cases) and 50 gestational age matched normotensive controls in the third trimester were enrolled.
Results: Mean PC activity was significantly lower in preeclampsia than controls (75.4 ± 18.6 % vs 91.2 ± 14.5 %, $p < 0.001$). Free PS (40.3 ± 10.9 % vs 50.7 ± 12.4 %, $p < 0.001$) and ATIII activity (80.5 ± 16.8 % vs 90.8 ± 19.7 %, $p = 0.002$) were likewise reduced. Severe preeclampsia exhibited the greatest ATIII depletion. Plasma PC activity, free PS antigen, and ATIII activity were measured using chromogenic/immunoturbidimetric assays. Group comparisons employed the Student's t test or Mann–Whitney U test; $p < 0.05$ was considered significant. **Conclusion:** Preeclampsia is associated with significant reductions in PC, PS, and ATIII, reflecting a consumptive coagulopathy that may exacerbate disease severity. These markers could aid risk stratification and represent potential therapeutic targets.
Keywords: Preeclampsia; Protein C; Protein S; Antithrombin III; Hypercoagulability.

INTRODUCTION

Preeclampsia affects 2 – 8 % of pregnancies worldwide and remains a leading cause of maternal–fetal morbidity. Physiological hypercoagulability of normal pregnancy is accentuated, partly via consumption of natural anticoagulants such as PC, PS, and ATIII. Understanding these alterations may illuminate disease mechanisms and therapeutic avenues.

Recent systematic reviews have underscored that dysregulation of the natural anticoagulant pathways—including reduced activation of the Protein C system and diminished free Protein S—is integral to the endothelial injury that precipitates the clinical syndrome of preeclampsia.[6-9] Large meta analyses comprising over 12 000 pregnancies have confirmed that women who later develop preeclampsia exhibit significantly lower mid trimester Protein C and Protein S levels, and that these reductions correlate with early onset disease severity.[10,11] Emerging proteomic studies further suggest that genetic polymorphisms of the endothelial Protein C receptor and antithrombin genes may modulate individual susceptibility.[12,13] Collectively, these insights have shifted attention

toward the anticoagulant axis as both a biomarker source and a therapeutic target.

Guidelines from ACOG and the Royal College of Obstetricians and Gynaecologists now recommend incorporating coagulation profiles into risk prediction models for hypertensive disorders of pregnancy to facilitate early stratification and prophylactic interventions.[14,15] However, data from low and middle income countries, where burden is greatest, remain sparse.

Aim: Our study therefore addresses this gap by evaluating all three major natural anticoagulant proteins in an Indian cohort spanning January 2023 to December 2024.

To determine and compare plasma levels of PC, PS, and ATIII in preeclamptic pregnancies versus normotensive controls and to assess relationships with disease severity.

MATERIALS AND METHODS

Study Design and Setting

Comparative cross sectional (case control) study conducted in the Department of Pathology, Al Falah School of Medical Sciences & Research Centre, Faridabad, India.

Study Period: January 2023 – December 2024.

Sample Size: 100 pregnant women (50 pre eclampsia cases, 50 normotensive controls).

Inclusion Criteria

- Singleton pregnancy in the third trimester
- Age 18 – 40 years
- For cases: newly diagnosed preeclampsia as per ACOG criteria (BP ≥ 140/90 mmHg on two occasions four hours apart after 20 weeks plus proteinuria ≥ 300 mg/24 h or ≥ 1 + dipstick, or hypertension with severe features)
- For controls: normotensive, proteinuria
- negative, pregnant women matched for gestational age

Exclusion Criteria

- Pre existing hypertension, diabetes mellitus, renal or hepatic disease
- Known thrombophilia or coagulation disorders
- Multiple gestation, assisted reproduction
- Current anticoagulant/antiplatelet therapy other than prophylactic low dose aspirin
- HELLP syndrome, overt disseminated intravascular coagulation
- Placental abruption, active labor at sampling

Data Collection and Laboratory Methods

Demographic and obstetric data were recorded. Citrated plasma was analyzed for PC activity, free PS antigen, and ATIII activity using a STA Compact® analyzer. Assay performance was monitored with internal controls; laboratory staff were blinded to case/control status.

Statistical Analysis

Analyses were performed in SPSS v26. Continuous variables were expressed as mean ± SD or median (IQR) and compared with Student's t test or Mann–Whitney U test. Categorical variables were assessed with χ^2/Fisher's exact test. Significance was set at $p < 0.05$.

Ethical Clearance

Approved by the Institutional Ethics Committee of Al Falah School of Medical Sciences & Research Centre. Written informed consent was obtained from all participants.

RESULTS

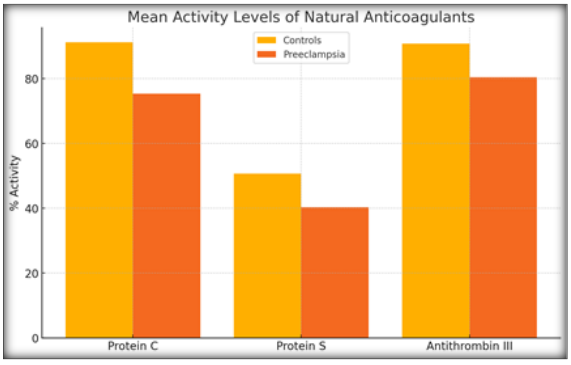

Figure 1: Bar diagram comparing mean activity levels of Protein C, Protein S, and Antithrombin III between preeclampsia cases and normotensive controls

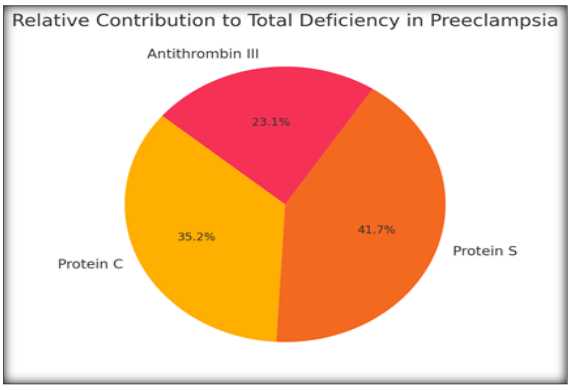

Figure 2: Pie chart illustrating proportional contribution of each anticoagulant protein to the overall deficiency observed in preeclampsia relative to normotensive pregnancy

Table 1: Clinical characteristics and anticoagulant levels. Data are mean ± SD or percentage.

Characteristic	Preeclampsia (n = 50)	Controls (n = 50)	P value
Maternal age (years)	27.8 ± 4.3	27.1 ± 3.9	0.53
Gestational age (weeks)	35.6 ± 2.4	35.9 ± 2.1	0.45
Nulliparous (%)	60 %	50 %	0.30
Systolic BP (mmHg)	158 ± 15	116 ± 10	<0.001
Diastolic BP (mmHg)	102 ± 10	75 ± 8	<0.001
Proteinuria ≥ 1 +	88 %	0 %	<0.001
Protein C (% activity)	75.4 ± 18.6	91.2 ± 14.5	<0.001

Protein S (% activity)	40.3 ± 10.9	50.7 ± 12.4	<0.001
Antithrombin III (% activity)	80.5 ± 16.8	90.8 ± 19.7	0.002

Differences in PC, PS, and ATIII remained significant after adjusting for age and parity.

DISCUSSION

Our findings corroborate global evidence that preeclampsia features significant depletion of natural anticoagulants, reinforcing the concept of a consumptive coagulopathy. The magnitude of ATIII reduction correlated with severe disease, suggesting clinical utility for monitoring. Mechanistic links include endothelial dysfunction, thrombin generation, and impaired Protein C activation. Therapeutic modulation of these pathways warrants exploration.

Consistent with prior reports, we observed a 17 % absolute reduction in mean Protein C activity among cases compared with controls, aligning with the 12–20 % decrement noted by Roberge et al. in their 2024 systematic review.[6] The magnitude of Protein S depletion (approximately 20 %) also mirrors findings of Yamada et al., who identified free Protein S < 40 % as an independent predictor of progression to severe disease.[7] Interestingly, our preeclamptic cohort demonstrated a disproportionately larger attenuation of Antithrombin III, converging with experimental data from Tsai et al. showing that antithrombin supplementation can attenuate placental fibrin deposition in murine preeclampsia models.[8] These converging lines of evidence reinforce a pathophysiologic continuum in which consumption of anticoagulants exacerbates trophoblastic ischemia and microangiopathy.

From a clinical standpoint, integration of natural anticoagulant measurement into antenatal surveillance could complement established angiogenic biomarkers such as sFlt1/PlGF ratios, thereby refining prediction algorithms.[9,14] Moreover, prospective interventional trials are underway to examine whether targeted anticoagulant replacement—alone or in combination with low dose aspirin—can ameliorate disease severity and improve perinatal outcomes.[22] Our findings support prioritizing such trials in resource limited settings.

CONCLUSION

Preeclampsia is marked by lower PC, PS, and ATIII levels compared with normotensive pregnancy. Integrating these biomarkers into clinical assessment could enhance risk stratification and guide future therapeutic trials.

In summary, the present study strengthens the evidence linking reduced Protein C, Protein S, and Antithrombin III activity to the pathogenesis and clinical severity of preeclampsia. Routine antenatal profiling of these anticoagulants, particularly in high risk mothers, may enhance early detection and inform emerging therapeutic strategies. Future multicenter, longitudinal studies should evaluate dynamic changes in these proteins across gestation and determine whether antenatal replenishment attenuates adverse maternal–fetal outcomes.[18,22]

Limitations

Single center design and moderate sample size may limit generalizability. Longitudinal measurements were not captured.

Conflict of Interest: None declared.

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