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Original Research

Glycosaminoglycan Matrix Exchange Imbalance in Preeclampsia: Correlation With Uteroplacental and Fetoplacental Hemodynamics

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Abstract

Background: Preeclampsia (PE) disrupts extracellular matrix homeostasis. However, the relationship between glycosaminoglycan (GAG) metabolic disturbances and their downstream hemodynamic consequences has not been systematically characterized across the full spectrum of PE severity. **Methods:** This retrospective cohort study used routine clinical data that had been collected prospectively between January 2023 and December 2024. It included 100 pregnant women with preeclampsia (PE) at 30 to 36 weeks of gestation and 30 normotensive controls. Under Chinese national obstetric guidelines, 50 women had mild PE, 30 moderate, and 20 severe. The primary outcomes were biochemical: total serum sulfated GAG concentration, chondroitin sulfate fractions, glycoprotein levels, and urinary hydroxyproline and uronic acid excretion. Secondary outcomes were uteroplacental and fetoplacental blood flow on Doppler ultrasonography, and fetal well-being by cardiotocography and biophysical profile (BPP) score. We compared groups with one-way analysis of variance (ANOVA) and Bonferroni post hoc tests for normally distributed data, or the Kruskal-Wallis test with Dunn post hoc tests otherwise. For the five primary outcomes, we used a Bonferroni-corrected omnibus threshold of $p < 0.01$ and judged pairwise comparisons at $p < 0.00167$. Secondary hemodynamic and fetal outcomes used the conventional $p < 0.05$ and should be read as exploratory. **Results:** Total serum sulfated GAG fell as PE worsened (controls 12.60 ± 0.40 U; severe PE 11.47 ± 0.35 U; $F(3,126) = 44.89$, $p < 0.001$). Chondroitin-4-sulfate (CS-4S) and fraction III (HS/DS/KS) decreased with severity, while chondroitin-6-sulfate (CS-6S) rose. Serum glycoprotein and urinary hydroxyproline and uronic acid were higher in every PE group than in controls ($p < 0.005$), which suggests faster connective tissue breakdown. On Doppler, uteroplacental abnormalities were more common than fetoplacental ones, yet all 20 women with severe PE (100%) had impairment in both. Intrauterine growth restriction (IUGR) became more frequent with severity: 12.0% in mild, 23.3% in moderate, and 40.0% in severe PE. Moderate versus mild did not reach significance (Fisher's exact test, $p = 0.21$), but severe versus mild did ($p = 0.02$). This finding in the severe group is exploratory. BPP scores fell steadily as severity increased. **Conclusions:** PE is associated with a severity-dependent GAG imbalance characterized by depletion of CS-4S and fraction III (HS/DS/KS) alongside accelerated extracellular matrix catabolism. These biochemical alterations are quantitatively associated with deterioration in uteroplacental and fetoplacental hemodynamics. Whether monitoring of GAG fractions can complement conventional PE markers to enable earlier detection of placental compromise warrants prospective validation in larger, multicenter cohorts. Restoration of vascular GAG concentrations represents a biologically plausible hypothesis that merits evaluation in preclinical models prior to clinical translation.

Keywords: preeclampsia; glycosaminoglycans; connective tissue matrix; uteroplacental hemodynamics; fetoplacental hemodynamics; chondroitin sulfate; heparan sulfate; glycocalyx; Doppler ultrasonography

1. Introduction

Preeclampsia (PE) affects 2–8% of pregnancies worldwide and accounts for approximately 76,000 maternal and 500,000 perinatal deaths annually [1]. Its incidence has increased in recent decades, a trend attributed to improved diagnostic sensitivity, declining baseline maternal health, the growing burden of non-communicable disease, and psychosocial stress [1]. Most affected women develop organ dysfunction involving the kidneys, liver, lungs, or brain, accompanied by metabolic and hemostatic disturbances [2].

At the core of PE pathophysiology lies impaired trophoblast invasion of the spiral arteries during early placentation. Failure to remodel these vessels into low-resistance conduits sustains vasoconstriction, thereby reducing uteroplacental blood flow. The resulting placental ischemia drives systemic release of anti-angiogenic factors and inflammatory mediators that damage the maternal endothelium, developing the clinical syndrome of hypertension, proteinuria, and multi-organ dysfunction [3]. Hemostatic dysregulation and circulatory compromise follow, with risk of fetal growth restriction and, in severe cases, fetal death [4,5]. Four principal mechanisms have been implicated in the PE pathogenesis: genetic predisposition, placental ischemia, oxidative stress, and immunological maladaptation

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[5]. These mechanisms converge on connective tissue and vascular biology, disrupting extracellular matrix homeostasis and endothelial function.

Glycosaminoglycans (GAGs), including hyaluronic acid, chondroitin sulfate, heparin, and heparan sulfate (HS), modulate endothelial surface charge and water-electrolyte permeability, and possess anticoagulant activity that protects the vascular endothelium [6,7,8]. GAGs are integral components of the glycocalyx covering the microvilli of the syncytiotrophoblast (STB), which lies in direct contact with maternal blood within the intervillous space (IVS). Disruption of this glycocalyx is an early indicator of endothelial pathology and is closely associated with endothelial dysfunction [7,8,9].

Sulfated GAGs regulate angiogenesis, modulate water-electrolyte balance, and limit albumin leakage. Chondroitin-4-sulfate (CS-4S) participates in hemostasis [6,7]. HS acts as an anticoagulant, promotes fibrinolysis, and functions as a mechanoreceptor [6,10]. Dermatan sulfate (DS) contributes to thrombus dissolution and prophylaxis [6]. Hyaluronic acid mediates shear-induced release of endothelium-derived nitric oxide [11].

Despite the established roles of GAGs in endothelial and placental biology, systematic assessment of their metabolic profiles in PE, and of the relationship between glycosaminoglycan (GAG) disturbances and measurable hemodynamic consequences, remains inadequate. A 2025 systematic review and meta-analysis reported a trend toward increased maternal serum HS in PE, with statistical significance reached in the early-onset PE subgroup (standardized mean difference [SMD]: 1.05; 95% confidence interval [CI]: 0.22–2.32) [12]. Elevated DS alongside decreased keratan sulfate (KS) has been reported in preeclamptic versus normotensive pregnancies, with DS inversely correlated with blood pressure (BP) [13]. Low soluble syndecan-1 (SDC1) has been shown to precede the clinical onset of PE, and reduced placental SDC1 expression has similarly been observed, together suggesting a role for glycocalyx disturbance in PE pathophysiology [14]. A 2019 study using sidestream dark field imaging reported glycocalyx degradation and reduced microvascular perfusion in early-onset PE, accompanied by elevated circulating HS proteoglycans and hyaluronic acid [15]. A 2026 comprehensive review provided evidence that endothelial glycocalyx damage underlies the generalized endothelial dysfunction observed in PE, linking glycocalyx disruption to the clinical manifestations across all maternal organ systems [9]. The present study addresses this gap by characterizing GAG metabolic profiles alongside Doppler-derived hemodynamic parameters across the spectrum of PE severity. Although some of the foundational biochemical methods are long established, recent systematic reviews confirm that GAG dysregulation in PE remains an active area of investigation with unresolved clinical questions, justifying continued study of these analytes [12,16].

Herein, we aimed to: (i) characterize the GAG exchange system of the connective tissue matrix in pregnant women with PE of varying severity; (ii) evaluate how alterations in GAG metabolism correlate with uteroplacental and fetoplacental hemodynamic parameters; and (iii) determine the association between GAG exchange disturbances and PE severity.

2. Materials and Methods

2.1 Study Design

This retrospective cohort study analyzed recorded routine antenatal clinical data collected from January 2023 to December 2024 at the College of Medicine. Biochemical and Doppler assessments were performed as part of standardized routine antenatal care, and the resulting data were subsequently extracted, anonymized, and analyzed for research purposes. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2 Participant Inclusion and Classification

100 pregnant women with PE of varying severity, at 30–36 weeks of gestation, were enrolled consecutively through routine antenatal screening. PE severity was classified according to the 2020 Chinese guidelines [17] as follows: Group I, mild PE (n = 50), defined as BP 140–159/90–109 mmHg with proteinuria <0.3 g/24 h at the time of diagnosis; Group II, moderate PE (n = 30), defined as BP 140–159/90–109 mmHg with proteinuria 0.3–2.9 g/24 h; and Group III, severe PE (n = 20), defined as BP ≥160/110 mmHg and/or proteinuria ≥3.0 g/24 h, or presence of any severe feature.

Classification With International Guidelines

The three-tier Chinese classification system does not map directly to the American College of Obstetricians and Gynecologists (ACOG)/the International Society for the Study of Hypertension in Pregnancy (ISSHP) binary classification system (PE without severe features vs. PE with severe features) [17]. For reference, Groups I and II (mild and moderate PE, n = 80) broadly correspond to “PE without severe features”, whereas Group III (severe PE, n = 20) broadly corresponds to “PE with severe features”. However, this mapping is not exact, as the Chinese moderate PE category includes some patients who may be classified differently under ACOG criteria. A secondary analysis comparing the merged binary strata for primary biochemical outcomes is provided in **Supplementary Table 1**. The findings were consistent with those of the primary three-tier analysis. This difference in classification systems is acknowledged as a limitation affecting direct comparison with studies using international classification criteria. A normotensive control group comprising 30 pregnant women with singleton pregnancies, matched for gestational age, was enrolled from the same antenatal clinic.

Table 1. Baseline demographic and clinical characteristics of the study population (mean ± SD or n [%]).

Characteristic	Controls (n = 30)	Mild PE (n = 50)	Moderate PE (n = 30)	Severe PE (n = 20)
Age (years)	26.8 ± 4.2	27.2 ± 4.8	27.6 ± 4.5	28.1 ± 4.3
Gestational age (weeks)	33.0 ± 1.7	33.1 ± 1.9	33.4 ± 1.8	33.5 ± 1.6
Nulliparous, n (%)	18 (60.0)	31 (62.0)	18 (60.0)	13 (65.0)
Family history of PE, n (%)	3 (10.0)	21 (42.0)	15 (50.0)	11 (55.0)
Systolic BP (mmHg)	118 ± 8	148 ± 10	158 ± 12	174 ± 14
Diastolic BP (mmHg)	74 ± 6	96 ± 8	104 ± 9	114 ± 11
Proteinuria (g/24 h)†	0.08 ± 0.03	0.32 ± 0.12	1.85 ± 0.64	4.20 ± 1.30

†Proteinuria values represent measurements obtained at study enrollment (30–36 weeks) and may differ from those at the time of the initial diagnosis. The diagnostic criterion for mild PE (<0.3 g/24 h) was applied at the time of diagnosis; the enrollment mean of 0.32 ± 0.12 g/24 h in Group I reflects the well-documented progressive nature of proteinuria in PE over the interval between diagnosis and later gestation and does not indicate misclassification. Maternal BMI and smoking status were not systematically recorded in the clinical database and therefore could not be adjusted for. Blood pressure and proteinuria are classification criteria; between-group comparisons are therefore descriptive and were not formally tested. PE, preeclampsia; BP, blood pressure; SD, standard deviation; BMI, body mass index.

Inclusion criteria were as follows: singleton pregnancy; gestational age 30–36 weeks; diagnosis of PE mild PE group (n = 50); the moderate PE (n = 30), severe PE (n = 20) or uncomplicated normotensive pregnancy (controls); and absence of concurrent systemic disease other than PE.

Exclusion criteria were as follows: 3 multiple pregnancy; 4 preexisting hypertension; 1 diabetes mellitus; 2 renal disease; 1 autoimmune disorders; and 3 any condition capable of independently affecting GAG metabolism or placental blood flow.

2.3 Sample Size

The sample size was estimated a priori based on the primary comparison of total serum GAG concentrations. Assuming a moderate effect size (Cohen's d = 0.6), two-sided alpha = 0.05, and 80% power, a minimum of 44 participants per comparison group was required. This target was met only for the mild PE group (n = 50). The moderate PE (n = 30), severe PE (n = 20), and control (n = 30) groups did not meet this threshold. Therefore, comparisons involving these subgroups should be considered exploratory, and non-significant findings interpreted cautiously as potentially underpowered rather than as definitive evidence of no effect. For the five primary biochemical outcomes, a Bonferroni-corrected omnibus threshold of $p < 0.01$ was applied, with pairwise post hoc comparisons evaluated at $p < 0.00167$.

2.4 Participant Characteristics

Baseline demographic and clinical characteristics of all study groups are presented in Table 1.

2.5 Biochemical Assessment of GAG Metabolism

Connective tissue matrix metabolism was characterized by measuring the total concentration of sulfated GAGs in serum using the alcian blue precipitation colorimetric assay, with results expressed in arbitrary units relative to a chondroitin sulfate A standard curve. Serum GAGs were fractionated into three groups: fraction I (chondroitin-6-sulfate, CS-6S), fraction II (chondroitin-4-sulfate, CS-4S), and fraction III (the poorly soluble heparan sulfate/dermatan sulfate/keratan sulfate pool, HS/DS/KS). Individual HS, DS and KS were not resolved separately; fraction III is therefore reported and interpreted as one combined fraction [18]. Total chondroitin sulfate was measured by the Rivanol precipitation method [19]. Glycoprotein concentrations were determined by the turbidimetric method [18]. Urinary hydroxyproline levels were measured by spectrophotometry [20]. GAG metabolic turnover was assessed by measuring urinary uronic acid concentration using the carbazole reaction [21]. All assays were performed in duplicate. The intra-assay coefficient of variation (CV) did not exceed 5%, and the inter-assay CV was below 8%. These methods predate contemporary liquid chromatography-tandem mass spectrometry (LC-MS/MS) and immunoassay-based approaches for GAG quantification. Although the reported CVs confirm adequate reproducibility within this study, validation using contemporary quantification methods is warranted in future work.

2.6 Hemodynamic Assessment

Uteroplacental and fetoplacental hemodynamics were evaluated by pulsed-wave Doppler ultrasonography. Blood flow velocity waveforms were recorded from both uterine arteries, the spiral arteries, the umbilical artery, and the fetal middle cerebral artery. The primary Doppler indices included the resistance index (RI) [22], pulsatility index (PI) [23], and systolic-to-diastolic (S/D) ratio [24]. Hemodynamic impairment was classified as compensated, subcompensated, or decompensated based on established reference ranges [5]. Fetal well-being was assessed by indirect cardiotocography [25,26] and the biophysical profile (BPP) using the modified six-component Vintzileos method [27].

Table 2. Concentrations of connective tissue matrix components by study group (mean ± SD).

Clinical group	Total sulfated GAG Arbitrary Units (U)	Chondroitin sulfate (g/L)	Glycoproteins (U)	Hydroxyproline (mg/day)	Uronic acid (mg/day)
Controls (n = 30)	12.60 ± 0.40	0.105 ± 0.030	0.35 ± 0.06	26.00 ± 3.50	4.00 ± 0.40
Mild PE (n = 50)	12.38 ± 0.45	0.280 ± 0.025[a]	0.55 ± 0.08[a]	47.86 ± 4.85[a]	6.44 ± 0.46[a]
Moderate PE (n = 30)	11.79 ± 0.35[a]	0.330 ± 0.030[a]	0.78 ± 0.06[a,b]	61.00 ± 5.40[a,b]	6.93 ± 0.40[a]
Severe PE (n = 20)	11.47 ± 0.35[a]	0.276 ± 0.030[a]	0.66 ± 0.06[a]	66.57 ± 4.80[a]	6.43 ± 0.40[a]
ANOVA F (df = 3)	44.89	370.39	210.08	397.53	294.91
Overall *p*-value	<0.001	<0.001	<0.001	<0.001	<0.001
η^2	0.517	0.898	0.833	0.904	0.875
Cohen's d (severe PE vs. control)	−2.97	5.70	5.17	9.98	6.07

F statistics are from one-way ANOVA with df = 3,126 (k = 4 groups, N = 130). F was computed as F = MS_between / MS_within, where MS_between = Σ n_g (M_g − M_grand)^2 / (k − 1) and MS_within = Σ (n_g − 1) SD_g^2 / (N − k). η^2 was computed as η^2 = SS_between / SS_total. Cohen's d was computed for the severe PE group versus controls as d = (M_severe − M_control) / SD_pooled, where SD_pooled = $\sqrt{[((n_1 - 1)\ SD_1^2 + (n_2 - 1)\ SD_2^2) / (n_1 + n_2 - 2)]}$. All input means and SDs are those shown in the table. [a]$p < 0.005$ versus controls; [b]$p < 0.005$ versus mild PE (Bonferroni-adjusted post hoc tests). All variables met assumptions for parametric testing; no variable was analyzed non-parametrically. GAG, glycosaminoglycan; MS, mean square; SS, sum of squares.

2.7 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD). The primary outcomes were the five biochemical GAG markers, and the secondary outcomes were hemodynamic and fetal parameters. Normality of each continuous variable within each group was assessed using the Shapiro–Wilk test ($p > 0.05$ taken as normal), supplemented by visual inspection of Q–Q plots; homogeneity of variance was assessed with Levene's test. Variables meeting both assumptions were analyzed by one-way ANOVA with Bonferroni post hoc tests; otherwise, Kruskal–Wallis with Mann–Whitney U post hoc tests (Bonferroni-adjusted) were used. Variables analyzed non-parametrically are identified in Table 2. Two-group comparisons were performed using Student's *t*-test. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Effect sizes are reported as η^2 for omnibus ANOVA comparisons, Cohen's d for named pairwise contrasts, and Spearman rho for correlation analyses. For the five primary biochemical outcomes, a Bonferroni-corrected omnibus threshold of $p < 0.01$ was applied, with pairwise post hoc comparisons evaluated at $p < 0.00167$; the conventional $p < 0.05$ was retained for secondary comparisons, which should be interpreted as exploratory. Confidence intervals for proportions were calculated using exact Clopper–Pearson intervals. Spearman rank correlations between GAG fractions and Doppler indices are presented as unadjusted exploratory associations; adjusted partial correlations were not feasible due to small within-stratum sample sizes (see Limitations). No primary outcome data were missing. All statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) for exact binomial confidence intervals and pairwise post hoc verification.

3. Results

3.1 Connective Tissue Matrix Metabolism

Women with PE exhibited a connective tissue matrix metabolic profile characterized by elevated serum glycoprotein concentrations and increased urinary excretion of hydroxyproline and uronic acids, consistent with increased extracellular matrix degradation. Total serum sulfated GAG concentrations progressively declined with increasing PE severity, reaching the corrected significance threshold ($p < 0.005$) in the moderate and severe PE groups. These findings are summarized in Table 2.

3.2 Fractional GAG Composition

Fractionation of serum sulfated GAGs revealed a progressive increase in the relative levels of CS-6S with increasing PE severity, alongside reductions in CS-4S and the poorly soluble fraction, comprising HS, DS, and KS (Fig. 1). The distribution of GAG fractions differed significantly between groups ($\chi^2 = 34.2$, $p < 0.001$ for all comparisons versus controls). As CS-4S is a major structural component of the vascular wall [7,28] and fraction III, which includes HS, the principal endothelial glycocalyx constituent [9,10], their concurrent reduction is consistent with both functional and structural endothelial damage [9].

Spearman rank correlation analysis showed an inverse association between the CS-4S fraction and uterine artery resistance index (rho = −0.52, $p < 0.001$), as well as between the fraction III (HS/DS/KS) and the umbilical artery PI (rho = −0.47, $p < 0.001$). These findings represent unadjusted exploratory associations. Because both GAG depletion and Doppler abnormalities become more pronounced with increasing PE severity, these correlations may reflect shared association with disease severity (ecological confounding) rather than a direct biological relationship. Adjusted partial correlation analyses were not feasible due to

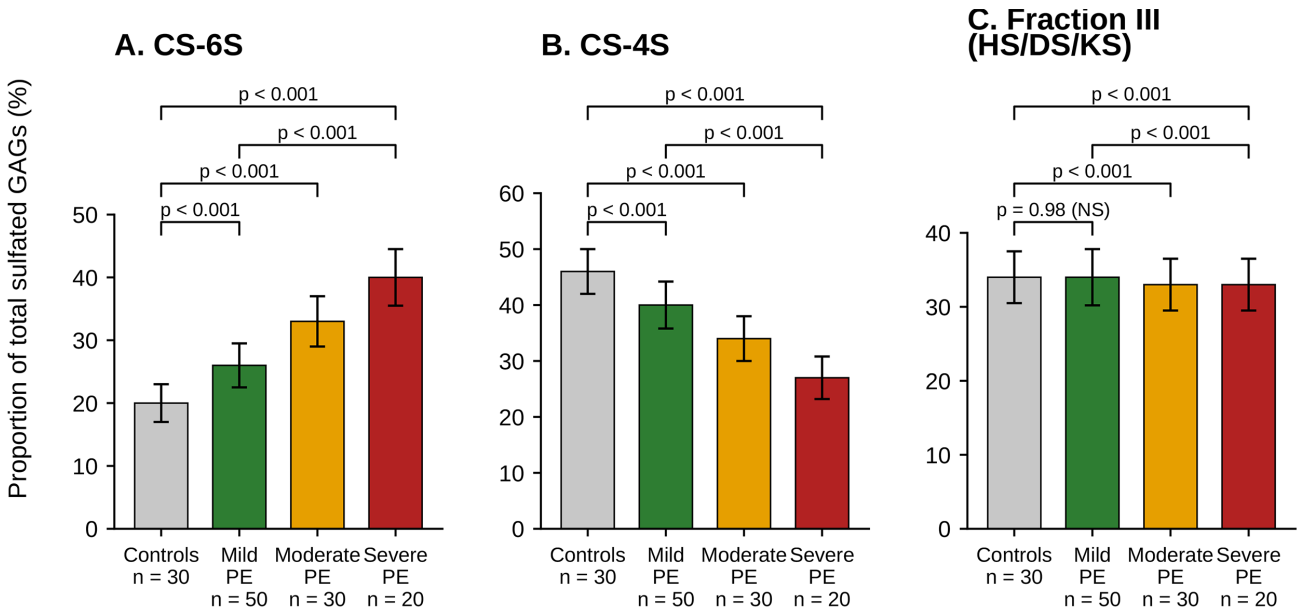


Fig. 1. Fractional composition of serum sulfated GAGs by study group. Panels show mean ± SD proportions of (A) chondroitin-6-sulfate (CS-6S), (B) chondroitin-4-sulfate (CS-4S), and (C) fraction III (HS/DS/KS) across controls (n = 30), mild PE (n = 50), moderate PE (n = 30), and severe PE (n = 20). Between-group differences were assessed by one-way ANOVA with Bonferroni post hoc tests. Panel A: $F(3,126) = 58.42$, $p < 0.001$, $\eta^2 = 0.582$. Panel B: $F(3,126) = 112.76$, $p < 0.001$, $\eta^2 = 0.729$. Panel C: $F(3,126) = 96.31$, $p < 0.001$, $\eta^2 = 0.697$. Error bars represent standard deviation. CS-6S, chondroitin-6-sulfate; CS-4S, chondroitin-4-sulfate; HS/DS/KS, heparan sulfate/dermatan sulfate/keratan sulfate; ANOVA, analysis of variance.

the small within-stratum sample sizes and are acknowledged as a limitation in Section 4.2.

3.3 Placental Morphology

Ultrasound examination showed a high frequency of pathological placental abnormalities in women with PE. Premature placental aging occurred in 11 of 50 women with mild PE (22.0%; 95% CI: 11.8–35.1%) compared with 2 of 30 normotensive controls (6.7%; 95% CI: 0.8–22.1%) ($\chi^2(1) = 3.24$, $p = 0.072$; Fisher's exact $p = 0.12$). Placental hypoplasia was identified in 7 mild-PE cases (14.0%; 95% CI: 5.8–26.7%) and 1 control participant (3.3%; 95% CI: 0.1–17.2%) (Fisher's exact $p = 0.24$). In severe PE, premature placental aging was detected in 11 of 20 participants (55.0%; 95% CI: 31.5–76.9%), placental hypoplasia in 8 (40.0%; 95% CI: 19.1–63.9%), and oligohydramnios in 9 (45.0%; 95% CI: 23.1–68.5%). Compensatory placental hyperplasia was identified in a subset of women with moderate and severe PE, consistent with an adaptive response to hemodynamic compromise [4,5]. IVS expansion in moderate and severe PE was consistent with impaired venous outflow and blood stasis [4,5].

3.4 Uteroplacental and Fetoplacental Hemodynamics

Placental dysfunction, defined by Doppler evidence of impaired uteroplacental or fetoplacental hemodynamics, increased progressively with PE severity. Placental dysfunction was identified in 22 of 50 women with mild PE (44.0%; 95% CI: 30.3–58.4%), 22 of 30 with moderate PE (73.3%; 95% CI: 54.1–87.7%), and all 20 women with severe PE (100%; 95% CI: 83.2–100%) ($\chi^2(2) = 21.07$, $p < 0.001$). Pairwise comparisons demonstrated differences between the mild vs. moderate PE groups (Fisher's exact $p = 0.011$), the moderate vs. severe PE groups (Fisher's exact $p = 0.007$), and the mild vs. severe PE groups (Fisher's exact $p < 0.001$); all pairwise tests were Bonferroni-adjusted ($\alpha = 0.017$).

Uterine artery blood flow showed side-to-side asymmetry even among normotensive controls, and this asymmetry was descriptively more marked in moderate and severe PE, a pattern compatible with impaired uteroplacental vascular adaptation [3,4]; however, these observational Doppler findings alone cannot establish the underlying mechanism, and the lateralization was not subjected to formal statistical testing.

In the mild PE group, Doppler evidence of uteroplacental hemodynamic impairment was detected in 19 of 50 participants (38.0%; 95% CI 24.7–52.8%), whereas fetoplacental disturbances were observed in 12 (24.0%; 95% CI 13.1–38.2%), Among these, 3 participants (6.0%; 95% CI 1.3–16.5%) exhibited isolated fetoplacental impairment, while 9 (18.0%; 95% CI 8.6–31.4%) demonstrated combined impairment.

In the moderate PE group, uteroplacental hemodynamic impairment was found in 21 of 30 participants (70.0%; 95% CI: 50.6–85.3%). Fetoplacental impairment

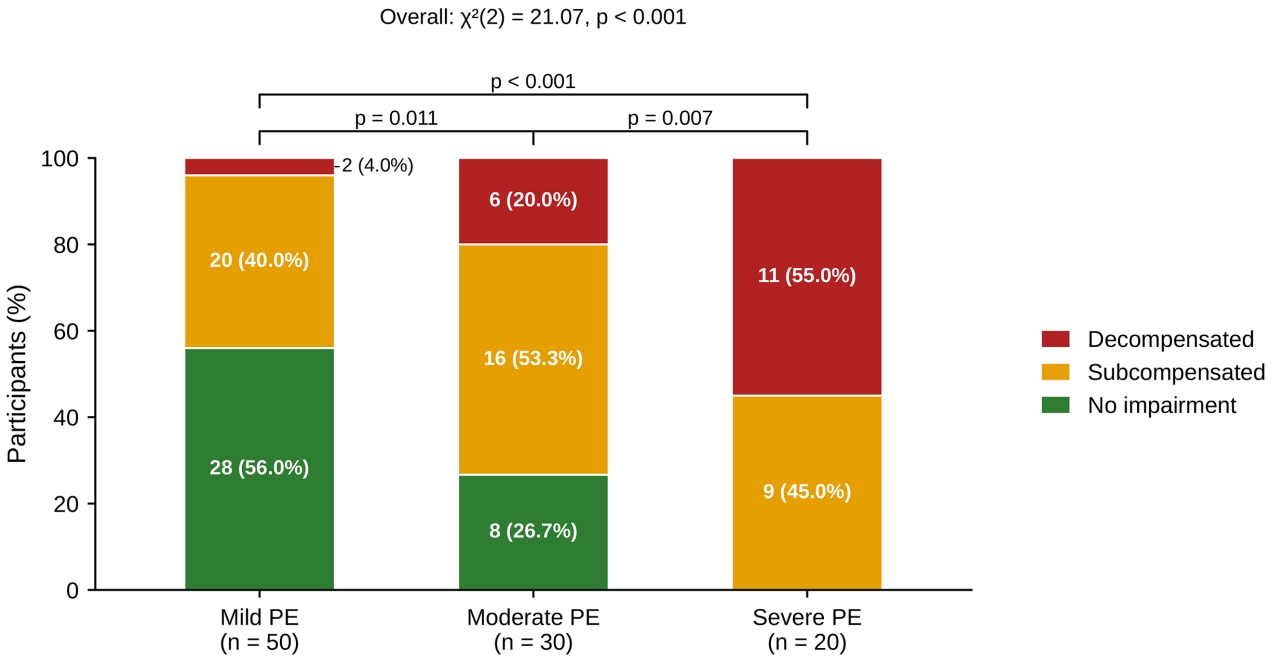


Fig. 2. Degree of uteroplacental blood flow impairment by PE severity. Values represent the proportion of participants with no impairment, subcompensated, or decompensated uteroplacental flow impairment in the mild PE (n = 50), moderate PE (n = 30), and severe PE (n = 20) groups. Overall between-group difference was assessed on the any-impairment contingency table: $\chi^2(2) = 21.07$, $p < 0.001$. Pairwise comparisons were performed using Fisher's exact test on any impairment, with Bonferroni adjustment ($\alpha = 0.017$): mild vs. moderate, $p = 0.011$; moderate vs. severe, $p = 0.007$; mild vs. severe, $p < 0.001$.

occurred in 20 participants (66.7%; 95% CI: 47.2–82.7%), including 1 participant (3.3%; 95% CI: 0.1–17.2%) with isolated impairment and 19 (63.3%; 95% CI: 43.9–80.1%) with combined impairment. Subcompensated fetoplacental hemodynamic abnormalities were more frequent than in mild PE group, and 3 cases (10.0%; 95% CI: 2.1–26.5%) showed decompensated fetoplacental blood flow.

In the severe PE group, all 20 participants (100%) exhibited combined uteroplacental and fetoplacental blood flow impairment, with a high prevalence of both subcompensated and decompensated blood flow abnormalities (Figs. 2,3).

3.5 Fetal Growth and Well-Being

The prevalence and severity of intrauterine growth restriction (IUGR) increased progressively with PE severity (Table 3). Overall, IUGR was identified in 12.0% of women with mild PE (95% CI: 4.5–24.3%), 23.3% of those with moderate PE (95% CI: 10.0–42.3%), and 40.0% of those with severe PE (95% CI: 19.1–63.9%). The difference in overall IUGR prevalence between the mild and moderate PE groups did not reach statistical significance ($\chi^2(1) = 1.77$, $p = 0.183$; Fisher's exact $p = 0.21$), whereas the prevalence was significantly higher in the severe than in the mild PE group (Fisher's exact $p = 0.02$). Grade II and III IUGR were not observed in the mild PE group but were present in both the moderate and severe PE groups.

Fetal BPP scores demonstrated a similar severity-dependent pattern. In normotensive controls, BPP scores ranged from 9 to 11. In mild PE, 36 of 50 participants (72.0%; 95% CI: 57.5–83.8%) had BPP scores of 7–9. In the moderate PE group, 23 of 30 (76.7%; 95% CI: 57.7–90.1%) had scores of 6–8. In contrast, 13 of 20 with severe PE (65.0%; 95% CI: 40.8–84.6%) had BPP scores below 6, prompting preterm delivery. The pattern of fetal deterioration was consistent with the staged model of fetal hypoxia [27], in which the loss of fetal heart rate reactivity preceded reductions in fetal respiratory and motor activity, with fetal tone decreasing last.

4. Discussion

This study demonstrates a systematic, severity-dependent disruption in GAG matrix homeostasis in pregnant women with PE that is quantitatively associated with progressive uteroplacental and fetoplacental hemodynamics. The principal biochemical finding was a progressive decline in the serum fractions of CS-4S and HS with increasing disease severity, accompanied by biochemical evidence of accelerated connective extracellular matrix catabolism, as reflected by elevated urinary excretion of hydroxyproline and uronic acids.

CS-4S is a major structural component of the vascular wall matrix [7,28]. HS is the principal constituent of the vascular glycocalyx [9] and plays essential roles in reg-

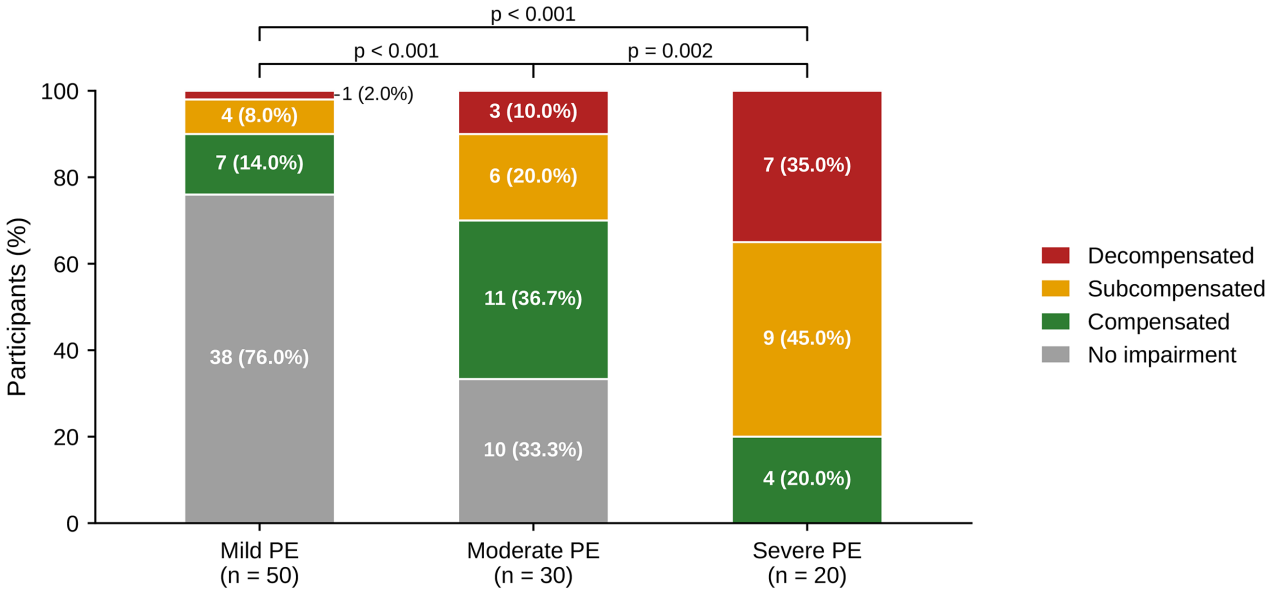


Fig. 3. Severity of fetoplacental blood flow impairment by PE severity. Values represent the proportion of participants with no impairment or with compensated, subcompensated, or decompensated fetoplacental flow impairment in the mild PE (n = 50), moderate PE (n = 30), and severe PE (n = 20) groups. All 20 women with severe PE (100%; 95% CI: 83.2–100%) showed combined uteroplacental and fetoplacental flow abnormalities. Statistical significance was observed across all pairwise comparisons (Fisher's exact test, Bonferroni-adjusted α = 0.017: mild vs. moderate, $p < 0.001$; mild vs. severe, $p < 0.001$; moderate vs. severe, $p = 0.002$). Uteroplacental impairment was more prevalent than fetoplacental involvement. CI, confidence interval.

Table 3. IUGR by PE severity.

Indicator	Mild PE (n = 50)	% (95% CI)	Moderate PE (n = 30)	% (95% CI)	Severe PE (n = 20)	% (95% CI)
IUGR — total	6	12.0 (4.5–24.3)	7	23.3 (10.0–42.3)	8	40.0 (19.1–63.9)
— Grade I	6	12.0 (4.5–24.3)	5	16.7 (5.6–34.7)	4	20.0 (5.7–43.7)
— Grade II	—	—	2	6.7 (0.8–22.1)	3	15.0 (3.2–37.9)
— Grade III	—	—	—	—	1	5.0 (0.1–24.9)

Note: *p*-values for the overall difference in IUGR prevalence compared with mild PE: moderate PE, $p = 0.21$ (NS); severe PE, $p = 0.02$ (Fisher's exact test). All 95% CIs were calculated using exact Clopper–Pearson intervals. NS, not significant; IUGR, intrauterine growth restriction.

ulating endothelial permeability [9], maintaining anticoagulant activity [6], and mediating endothelial responses to shear stress [10]. Concurrent depletion of CS-4S and fraction III (HS/DS/KS) may compromiseglycocalyx integrity on both STB microvilli and on maternal endothelial cells, leading to increased vascular permeability and disruption of the anticoagulant surface that protects against intervillous thrombosis [7,8,9,15]. The hemodynamic findings followed a similar severity-dependent pattern, with increasing uterine vascular resistance, reduced intervillous perfusion, and progressive impairment of fetoplacental circulation [3,4]. The observed Spearman rank correlations between GAG fractions and Doppler indices (CS-4S vs uterine artery RI: rho = −0.52, $p < 0.001$; fraction III (HS/DS/KS) vs umbilical artery PI: rho = −0.47, $p < 0.001$) further support this association. However, these findings should be interpreted with caution, as the observational study design precludes inference of causality, and the observed correlations may be partially explained by the shared association of both GAG depletion and Doppler abnormalities with increasing PE severity.

The severity-dependent shift in GAG composition, characterized by an increasing proportion of CS-6S relative to CS-4S, suggests that the predominant pathological process is the degradation of structural, poorly soluble GAG species [7,28] rather than a generalized suppression of GAG biosynthesis. Concurrent increase in urinary uronic acid excretion further reinforces this interpretation.

The nonmonotonic trend observed for total chondroitin sulfate concentration warrants careful consideration. Although the mean concentration in the severe PE group (0.276 ± 0.030 g/L) was numerically similar to that observed in the mild PE group (0.280 ± 0.025 g/L), it was lower than that observed in the moderate PE group (0.330 ± 0.030 g/L). Several explanations should be considered: (i) a floor effect resulting from accelerated systemic extracellu-

lar matrix catabolism, depleting circulating chondroitin sulfate in severe PE; (ii) increased renal clearance associated with the substantially higher proteinuria observed in severe PE (4.20 ± 1.30 g/24 h), potentially enhancing urinary GAG loss; (iii) assay saturation at intermediate analyte concentrations; or (iv) altered hepatic synthesis or processing of chondroitin sulfate. This pattern requires independent replication and should be interpreted with caution. Nevertheless, this observation further emphasizes that changes in the fractional composition of GAGs may represent a more sensitive indicator of disease severity than total GAG concentration alone.

The four principal mechanisms implicated in the pathogenesis of PE, namely genetic predisposition, placental ischemia, oxidative stress, and immunological maladaptation [5], are all relevant to GAG biology. Glycocalyx components are direct targets of oxidative injury [9,15], whereas CS-4S and HS contribute to the hemostatic and inflammatory responses associated with placental ischemia [6,9]. In addition, GAG biosynthesis may be regulated by angiogenic factors, including vascular endothelial growth factor (VEGF) and placental growth factor, both of which are known to be dysregulated in PE [3].

The biochemical methods employed in this study, including Alcian blue precipitation, Rivanol precipitation, and the carbazole reaction, are well established and have been extensively validated in the foundational literature. These assays demonstrated satisfactory analytical performance, with an intra-assay CV ≤5% and an inter-assay CV <8%. However, these techniques predate contemporary LC-MS/MS and immunoassay-based approaches, which offer higher analytical sensitivity, specificity, and structural characterization of individual GAG species. The consistency of our findings with those reported in more recent studies using modern analytical methods [12,13] supports their validity. However, independent replication using current high-resolution techniques is warranted.

Hassani Lahsinoui et al. [13] reported significantly elevated circulating DS concentrations in women with PE and demonstrated an inverse relationship between DS and BP. Soluble syndecan-1 was also identified as a mediator of soluble fms-like tyrosine kinase-1 (sFlt-1)-induced hypertension, with circulating levels declining after delivery, consistent with a placental origin. Gómez-Gutiérrez et al. [12] further confirmed this evidence in a 2025 systematic review and meta-analysis, demonstrating that maternal serum HS is significantly altered in PE, supporting the clinical relevance of the GAG-endothelial axis. In the present study, the combination of reduced CS-4S and fraction III alongside increased CS-6S suggests redistribution of GAG species.

4.1 Potential Confounders

Several potential confounders warrant consideration. Maternal body mass index (BMI), which influences both the risk of PE and connective tissue metabolism, was not systematically recorded in the clinical database and therefore could not be adjusted for. Similarly, data on smoking status, gestational weight gain, and socioeconomic characteristics were unavailable, precluding adjustment for these potential sources of confounding. The use of antihypertensive medications, magnesium sulfate, and antenatal corticosteroids, which was predominantly confined to the moderate and severe PE groups, may have independently affected both GAG metabolism and hemodynamic parameters. Given the observational study design, causal relationships cannot be established, and residual confounding cannot be excluded. Future prospective studies should systematically collect these treatment-related variables and incorporate them into multivariable adjusted models.

These findings have two potential clinical implications. First, prospective validation in larger, multicenter cohorts with appropriate statistical power is needed to determine whether monitoring the fractional composition of serum GAGs provides incremental value over conventional biomarkers for the early detection of hemodynamic deterioration. Second, therapeutic strategies aimed at preventing or restoring vascular GAGs represent a biologically plausible approach [9] warranting evaluation in preclinical models before any clinical translation.

4.2 Limitations

Several limitations should be acknowledged. (1) Single-center study design may limit the generalizability of the findings. (2) Subgroup analyses within the severe PE group (n = 20) had an estimated post hoc statistical power of approximately 62% to detect moderate effect sizes, underscoring the need for larger multicenter studies. (3) GAG measurements were performed at a single time point; longitudinal assessments throughout pregnancy would clarify the temporal relationships between alterations in GAG metabolism and hemodynamic deterioration. (4) Potential confounders, including maternal BMI, smoking status, medication use, and socioeconomic factors, were unavailable and could not be adjusted for. Proteinuria was measured at study enrollment rather than at the time of diagnosis. Accordingly, the mean proteinuria value in the mild PE group at enrollment was slightly above the diagnostic threshold, reflecting disease progression between diagnosis and measurement at 30–36 weeks rather than diagnostic misclassification. (5) Causality between GAG deficiency and hemodynamic impairment cannot be established from the observational design; in addition, uterine artery lateralization was assessed descriptively and side-specific RI values were not modeled longitudinally. (6) The GAG fractionation methods used in this study predate modern immunoassay and LC-MS/MS approaches, and future studies should validate findings using contemporary analytical techniques. (7) The three-tier Chinese classification system for PE [17] does not correspond directly to the binary criteria proposed by ACOG/ISSHP [1], limiting direct compar-

ison with international studies. (8) The reported Spearman rank correlations between GAG fractions and Doppler indices were unadjusted for PE severity. Because adjusted partial correlation analyses were not feasible due to the small within-stratum sample sizes, the possibility of ecological confounding cannot be excluded. (9) The nonmonotonic trend observed for total chondroitin sulfate concentrations requires independent replication. This finding may reflect differential renal clearance, assay saturation, or altered hepatic synthesis, rather than a simple catabolism floor effect.

5. Conclusions

In women with PE, CS-4S and fraction III (HS/D-S/KS) decline progressively with increasing disease severity, accompanied by accelerated extracellular matrix catabolism. These alterations are quantitatively associated with worsening uteroplacental hemodynamic dysfunction, fetal growth restriction, and declining BPP scores. Whether fractional GAG monitoring alongside standard markers can identify early placental dysfunction remains to be established through prospective validation in larger multicenter studies. Similarly, therapeutic strategies aimed at restoring vascular GAG homeostasis represent a biologically plausible approach that warrants evaluation in preclinical models before clinical translation. Collectively, these findings provide a hypothesis-generating framework to guide future prospective studies with sufficient statistical power.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

MAA: conceptualization, methodology, formal analysis, investigation, writing. WL: project administration, substantial contributions to the conception, analysis, interpretation of data for the work, supervision. MA, RAK: investigation, data collection. SQS: clinical assessment and analysis. All authors contributed to editorial changes in the manuscript. All authors reviewed and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Retrospective research analysis approved by the Biomedical Ethics Committee of the Affiliated Hospital of Hebei University of Engineering, College of Medicine (Approval No.: YS-YXY-2025005, January 2025). Participant consent for clinical assessments and potential research use of anonymized data was obtained during routine clinical care, in accordance with the institutional consent framework and the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

ChatGPT (GPT-5.6 Luna) were used for grammar and language editing only. All scientific content and conclusions are the original work of the authors. After using this tool, the authors carefully reviewed, revised, and approved the final content of the manuscript and take full responsibility for the integrity and accuracy of the work.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG54035.

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