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Plasma CD59 concentrations are increased in preeclampsia with severe features and correlate with laboratory measures of end-organ injury☆

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ABSTRACT

Objectives: Dysregulation of CD59 may lead to increased complement-mediated end-organ injury in preeclampsia. We sought to determine if soluble CD59 concentrations are altered in preeclampsia with severe features.

Study design: Observational case-control study, which enrolled subjects prospectively from six centers in Colombia from 2015 to 2016. Cases had preeclampsia with severe features and controls were either healthy or had chronic hypertension, gestational hypertension, or preeclampsia without severe features. Trained coordinators collected clinical data, blood and urine. Analyses were by test of medians and Spearman's correlation.

Main outcome measures: Soluble CD59 concentration in plasma and urine, using enzyme linked immunosorbent assays.

Results: In total, 352 subjects were enrolled (104 cases; 248 controls). Compared to healthy women or those with other hypertensive disorders of pregnancy, women with preeclampsia with severe features had increased concentration of CD59 in plasma ($P < 0.001$) and decreased CD59 in urine ($P = 0.01$). In sub-group analyses, plasma CD59 concentrations were increased in preeclampsia with severe features compared to healthy controls ($P < 0.001$) or controls with either chronic hypertension ($P = 0.002$) or gestational hypertension ($P = 0.02$). Increased plasma CD59 concentrations correlated with decreased platelet count and increased lactate dehydrogenase, creatinine, aspartate transaminase, urine protein/creatinine ratio, systolic blood pressure and diastolic blood pressure ($P < 0.01$, all correlations).

Conclusion: In women with preeclampsia with severe features, soluble CD59 concentrations were increased in plasma and decreased in urine, and plasma levels correlated with increased blood pressure and end-organ injury. Soluble CD59 concentrations may help identify a subset of women with preeclampsia that have altered regulation of terminal complement proteins.

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1. Introduction

Hypertensive disorders of pregnancy continue to be a leading cause of maternal morbidity and mortality worldwide [1]. Preeclampsia is a hypertensive disorder of pregnancy defined by elevated blood pressure with proteinuria or end-organ injury [2]. Variable organs may be affected by preeclampsia including the brain, endothelium, kidney, and liver, among others. When preeclampsia is complicated by end-organ injury, it is termed preeclampsia with severe features, and when there is microangiopathic hemolysis, elevated liver enzymes, and low platelet count it is termed HELLP syndrome [3]. While preeclampsia is characterized by a marked increase in circulating anti-angiogenic factors from the placenta, the factors involved in the progression of disease to end-organ injury and HELLP syndrome are less clear [4].

There is increasing recognition that the terminal complement pathway, part of the innate immune system, may have a potential role in the evolution of preeclampsia with severe features and HELLP syndrome [5–8]. Our prior work with the Complement and Preeclampsia in the Americas (COPA) study demonstrated that plasma and urine concentrations of C5b-9, a terminal complement effector, are increased among women with preeclampsia with severe features compared with other pregnant women [7]. Activated terminal complement proteins conduct a direct attack on the surface of cells, mediating the formation of the membrane attack complex (C5b-9), which is lytic and forms pores [9]. Even when C5b-9 deposition is sub-lytic, there are significant changes in cells that lead to proliferation, secretion of proinflammatory mediators and thrombosis [9,10]. For example, C5b-9 deposition in the placenta may lead to increased production and secretion of anti-angiogenic factors, which are implicated in preeclampsia [11]. Thus, the endogenous complement inhibitor CD59, a transmembrane protein responsible for regulating the action of C5b-9 in cell lysis through prohibiting the coupling of C9 to C5b-8 [12], may be critical to mitigating the harmful effects of C5b-9 deposition in preeclampsia (Fig. 1).

Terminal complement activation in preeclampsia with severe features may be due to increased complement activation, impaired complement regulation, or both. Considering that CD59 is the primary endogenous inhibitor of C5b-9 on the surface of endothelial and placental trophoblast cells [13–15], we hypothesized that dysregulation of CD59 may lead to greater complement-mediated end-organ injury in preeclampsia. We sought to test the hypothesis that serum and urine CD59 concentrations are altered in women with preeclampsia with severe features compared to pregnant women with other hypertensive disorders or those without hypertension.

2. Methods

The Complement and Preeclampsia in the Americas (COPA) study was a prospective, multicenter case-control study performed at six centers in Colombia from November 2015 to July 2016. Detailed methods have been described previously [7]. In this analysis, termed COPA-2 to distinguish it from our prior work, we measured soluble CD59 concentrations in plasma and urine from COPA study participants, using previously unthawed aliquots. Institutional review board approval was obtained specifically for the COPA-2 study at Universidad de Antioquia in Medellín, Colombia and all study sites: Clínica Reina Sofía – Sanitas and Hospital San Ignacio (Bogotá), Clínica Universitaria Bolivariana, Hospital Universitario San Vicente Fundación, and Hospital General de Medellín, (Medellín), E.S.E. Clinica de Maternidad Rafael Calvo (Cartagena). Subjects signed informed consent prior to study entry and all procedures were followed in accordance with institutional guidelines and study protocol.

In brief, eligible subjects were enrolled sequentially by trained research coordinators during available work hours. Cases were women with preeclampsia with severe features while controls could be healthy pregnancies, or those with chronic hypertension, gestational hypertension, or preeclampsia without severe features. Target enrollment was 100 cases of preeclampsia with severe features, with controls matched in 2:1 ratio to cases by gestational age category of the case (<34 or ≥34 weeks). Diagnoses, including the diagnosis of preeclampsia with severe features, were made in accordance with the 2013 American College of Obstetricians and Gynecologists' criteria for hypertension in pregnancy [2]. Severe features of preeclampsia included: two blood pressures ≥160 mmHg systolic or ≥110 mmHg diastolic measured four hours apart or multiple severe range blood pressures requiring acute

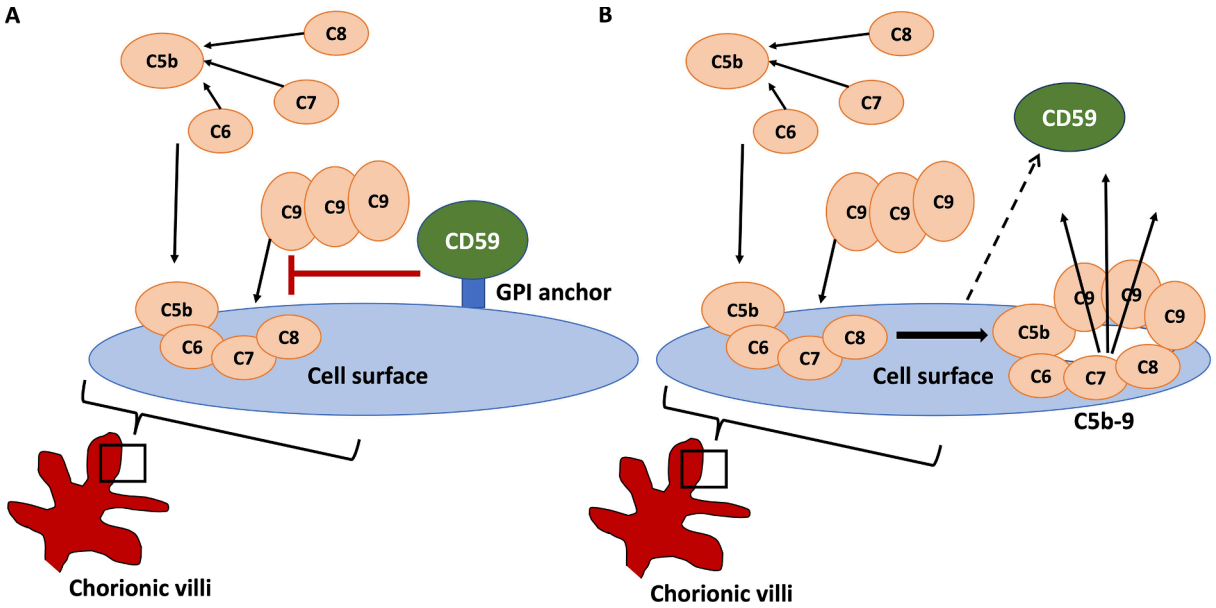

Fig. 1. Schematic diagram of the role of CD59 at the cell surface. Depicted is a placental villous stem (chorionic villi) with magnification to show deposition and regulation of terminal complement proteins on the syncytiotrophoblast cell surface. Enzymatic cleavage of C5 (not pictured) leads to generation of C5b, which combines with C6, C7, and C8 to form the C5b-8 complex on the cell surface. CD59, when expressed on the cell membrane and bound by a GPI anchor, blocks formation of C5b-9 on the cell surface by inhibiting the incorporation of C9 proteins into the C5b-9 complex. (A) When CD59 is released from the cell surface (dashed line) it no longer inhibits the union of C5b-8 to C9. This leads to formation of C5b-9 (membrane attack complex), a transmembrane pore which disrupts the cell membrane leading to cell lysis (black arrows).

treatment, alanine transaminase or aspartate transaminase ≥2x the upper limit of normal, creatinine > 1.1 mg/dl, platelet count <100 k/μl, pulmonary edema, severe headache or visual disturbances, and severe right upper quadrant or epigastric pain.

Subjects were enrolled from outpatient clinics, labor and delivery floors, antepartum units, and triage or emergency wards. Clinical diagnoses were confirmed within the first 24 h after enrollment once - blood pressure, laboratory values and symptoms were clarified. The normal reference range for standard blood tests at study sites were: aspartate transaminase (15–46 U/L); creatinine (0.5–1.1 mg/dl); lactate dehydrogenase (125–243 U/L); and platelet count (150–450,000/μl). Subjects were excluded for gestational age <24 weeks, uncertain dates, multifetal gestation (≥2), major chromosomal abnormality, fetal demise at entry, or inability to sign informed consent. Study data, including subject demographics, clinical history, laboratory data, and delivery and neonatal outcomes were recorded through standardized data collection forms and entered into a centralized electronic database.

The primary outcome was soluble CD59 concentrations in women in the case group compared with women in the control group. The secondary outcome was CD59 concentrations in women in the case group versus individual control subgroups. Blood and urine samples were collected from study subjects on the day of enrollment. Upon collection, samples were immediately centrifuged, with supernatant aliquoted and stored in cryovials at −70 to −80 °C, until CD59 assays could be performed. Soluble CD59 (CD59) was measured in plasma and urine by human CD59 glycoprotein enzyme-linked immunosorbent assay (MyBioSource, San Diego, CA). Assays were performed using a DSX automated 4-plate ELISA system (Dynex Technologies, Chantilly, VA) at Clínica ColSanitas in Bogotá, Colombia. Samples were run in duplicate with negative (blank) and positive controls (pooled plasma). Intra- and inter-assay coefficients of variation were 2.0% and 11.5%. Plasma samples were run after 1:2–1:100 dilution and urine samples at 1:2 dilution to obtain concentrations in the linear region of the standard curve. CD59 values within two standard deviations of the blank (<0.20 ng/ml) were considered below the lower limit of detection. After sample dilution, plasma and urine CD59 concentrations were in the range of detection for all subjects. Protein and creatinine concentrations were determined in urine samples by colorimetric assays (Roche/Hitachi Cobas c system, Roche Diagnostics, North America); Clínica ColSanitas, Bogotá).

COPA-2 was designed to test the hypothesis that soluble CD59 concentrations are in plasma and urine in women with preeclampsia with severe features compared to controls (healthy, chronic hypertension, gestational hypertension, preeclampsia without severe features). With 100 cases and 200 controls, the COPA-II study was powered to demonstrate a 50% difference in plasma CD59 concentrations and a 200% difference in urine CD59 concentrations between groups, with an alpha level of 0.05 and power equal to 0.80. Although there was a lack of preexisting pregnancy data, we anticipated a larger variation in urine CD59 concentrations due to the expected fluctuation in urine protein concentrations among preeclampsia subjects. It is known that cases of preeclampsia with severe features are more likely to present at an earlier gestational age compared to controls. Therefore, study sites were instructed to enroll cases and controls into stratified groups by gestational age (<34 weeks or ≥34 weeks) and diagnosis, until recruitment targets were met.

Baseline characteristics of study subjects were analyzed with descriptive statistics. Data normality was determined based on tests of skewness and kurtosis, with non-normal data displayed as medians (interquartile range, IQR). Data were analyzed by χ^2 test for dichotomous data, *t* test or analysis of variance for normal continuous data, and non-parametric equality of medians test or Spearman's correlation coefficient for non-normal continuous data. Analyses were performed with Stata software (StataCorp, College Station, TX), and statistical significance was determined by using an alpha level of 0.05.

3. Results

We enrolled 352 subjects, with the following distribution by study site: Hospital Universitario San Vicente Fundación (n = 85); Clínica Reina Sofía – Sanitas (n = 60); Clínica Universitaria Bolivariana (n = 58); E.S.E. Clinica de Maternidad Rafael Calvo (n = 53); Hospital Universitario San Ignacio (n = 49) and; Hospital General de Medellín (n = 47). Baseline characteristics of study subjects have been published previously and are presented in Table 1 [7].

Plasma CD59 concentrations were significantly increased in cases of preeclampsia with severe features compared to controls (healthy, chronic hypertension, gestational hypertension, or preeclampsia without severe features), [median (IQR): 32.0 (27.4–38.8) vs. 27.6 (22.4–34.6) ng/ml, P < 0.001]. In sub-group analyses, plasma CD59 concentrations were significantly increased in cases of preeclampsia with severe features compared to healthy controls (P < 0.001) or controls with either chronic hypertension (P = 0.002) or gestational hypertension (P = 0.02, Table 2). Plasma CD59 concentrations were also increased in subjects with preeclampsia without severe features compared to healthy controls (P = 0.02).

In contrast to plasma, urine CD59 concentrations were lower in cases of preeclampsia with severe features compared to controls (healthy, chronic hypertension, gestational hypertension, or preeclampsia without severe features), [median (IQR) 0.77 (0.57–1.1) vs. 0.94 (0.58–1.3) ng/ml, P = 0.01]. Similarly, the fractional excretion of CD59 (urine CD59/plasma CD59 × 100%) was also decreased in preeclampsia with severe features compared to controls, [median (IQR) 2.4% (1.5%–3.5%) vs. 3.3% (2.1%–4.8%), P = 0.001]. In sub-group analyses, urine CD59 concentration and fractional excretion of CD59 were decreased in preeclampsia with severe features compared to healthy controls (P = 0.02, Table 2).

In correlation analyses, plasma CD59 concentrations were significantly associated with laboratory measures of end-organ injury, including decreased platelet count (P < 0.001) and increased lactate dehydrogenase (P = 0.003), serum creatinine (P < 0.001), aspartate transaminase (P = 0.005) and urine protein/creatinine (P < 0.001), Table 3. However, urine CD59 concentrations did not correlate with any laboratory measures. Increased plasma CD59 concentrations correlated with increased systolic and diastolic blood pressure (P < 0.001 for both comparisons), while increased urine CD59 concentrations correlated with decreased systolic and diastolic blood pressure (P = 0.01 and P = 0.008, respectively).

4. Discussion

We found that concentrations of soluble CD59 were increased in plasma, and decreased in urine, in women with preeclampsia with severe features compared with women with other hypertensive disorders of pregnancy or women without hypertension. In pairwise comparisons, plasma and urine CD59 concentrations were not different in women with preeclampsia with or without severe features. However, increased plasma CD59 concentrations correlated with systolic and diastolic blood pressure and laboratory measures of end-organ injury, including those measures attributed to severe disease such as decreased platelet count and elevated liver enzymes.

The strengths of our study included its multicenter prospective case-control design, large number of subjects with preeclampsia with severe features, and gestational-age matched controls. Moreover, we included subjects with the full range of hypertensive disorders of pregnancy, allowing us to evaluate CD59 concentrations across the full spectrum of disease. Our study was limited by its observational design, which does not allow us to draw definitive conclusions regarding causal relationships. It remains unknown whether plasma CD59 concentrations increase, or urine CD59 concentrations decrease, prior to onset of clinical disease. We did not measure other soluble complement regulators (eg, complement factor H, complement factor I) that might influence

Table 1
Baseline characteristics of study subjects stratified by enrollment group.

Characteristic	Healthy (n = 54)	Chronic Hypertension (n = 50)	Gestational Hypertension (n = 87)	Preeclampsia without Severe Features (n = 57)	Preeclampsia with Severe Features (n = 104)	P*
Gestational age (wk)	34.2 ± 4.2	34.3 ± 4.2	35.5 ± 4.2	35.4 ± 3.7	33.2 ± 4.2	N/A†
Age (y)	30.2 ± 6.2	29.4 ± 6.8	26.5 ± 6.1	25.9 ± 6.8	25.7 ± 6.5	<0.001
BMI (kg/m^2)	23.8 ± 3.5	28.1 ± 5.5	25.4 ± 4.6	25.7 ± 5.0	24.7 ± 4.3	<0.001
Systolic BP (mmHg)	114 ± 13	139 ± 12	142 ± 11	141 ± 11	150 ± 16	<0.001
Diastolic BP (mmHg)	67.0 ± 9.4	85.4 ± 12	89.0 ± 7.7	88.0 ± 9.4	95.8 ± 13	<0.001
Urine protein/ creatinine (mg/mg)	0.10 (0.07–0.12)	0.12 (0.09–0.14)	0.12 (0.09–0.16)	0.37 (0.16–0.76)	0.91 (0.33–3.7)	<0.001
Nulliparous	32/52 (61.5)	26/50 (52.0)	57/83 (68.7)	46/57 (80.7)	65/103 (63.1)	0.03
African descent	1/49 (2.0)	5/49 (10.2)	19/83 (22.9)	9/56 (16.1)	19/103 (18.5)	0.02

N/A, not applicable; BMI, body mass index; BP, blood pressure. Data are mean ± SD, median (interquartile range), or n/N (%), unless otherwise stated. Reprinted with permission from Burwick RM, Velásquez JA, Valencia CM, et al. Terminal Complement Activation in Preeclampsia. Obstet Gynecol. 2018;132(6):1477–1485. Copyright © 2018, by the American College of Obstetricians and Gynecologists.
* Analysis of variance (means), χ^2 test (percentages), test of medians (non-parametric data).
† Enrollment in blocks by gestational age.

Table 2
Plasma and urine CD59 concentrations, and fractional CD59 excretion, by study group.

Measure	Healthy (n = 54)	CHTN (n = 50)	GHTN (n = 87)	PE (n = 57)	PE-SF (n = 104)	P*
Plasma CD59 ng/ml	23.7 (20–31)	27.5 (24–34)	29.2 (25–35)	28.3† (23–36)	32.0‡ (27–39)	0.001
Urine CD59 ng/ml	1.01 (0.7–1.4)	0.96 (0.7–1.1)	0.85 (0.5–1.2)	0.94 (0.6–1.4)	0.77§ (0.6–1.1)	0.01
Fractional Excretion CD59‖	3.89 (2.7–5.5)	3.46 (2.3–4.3)	2.73 (1.8–4.4)	3.19 (2.1–4.3)	2.39§ (1.5–3.5)	0.001

CHTN, chronic hypertension; GHTN, gestational hypertension; PE, preeclampsia without severe features; PE-SF, preeclampsia with severe features.
Data are median (interquartile range). Pairwise comparisons by Wilcoxon rank sum test and non-significant (P > 0.05) unless otherwise stated.
* PE-SF cases vs. all controls (Healthy, CHTN, GHTN, PE) by Wilcoxon rank sum test.
† P = 0.02, PE vs. Healthy.
‡ P < 0.001, PE-SF vs. Healthy; P = 0.003, PE-SF vs. CHTN; P = 0.02, PE-SF vs. GHTN.
§ P = 0.02, PE-SF vs. Healthy.
‖ Fractional excretion CD59 = (urine CD59/plasma CD59) × 100%.

complement activity in preeclampsia, but instead focused on CD59, which is the primary endogenous inhibitor of C5b-9 (terminal complement complex; membrane attack complex) [12,16]. Moreover, while prior studies have investigated other soluble complement regulators in preeclampsia, this was the first study to measure soluble CD59 concentrations in women with hypertensive disorders of pregnancy [17–19].

Our findings are consistent with other studies showing that impaired complement regulation is often present in women who develop preeclampsia with severe features or HELLP syndrome [20,21]. Similar to complement anaphylatoxins C3a and C4a, which are themselves vasoactive and have been shown to contribute directly to the manifestation of hypertension, the soluble forms of CD59 could play a role in this vasoactive response, given its humoral and cellular influence and other functions not yet clearly elucidated [22,23]. However, the ability of CD59 to inhibit terminal complement activation and C5b-9 associated cell lysis is greatest when it is anchored to the cell membrane [12]. In preeclampsia, C5b-9 deposition on the surface of endothelial and placental trophoblast cells may exceed the regulatory capacity of membrane-bound CD59, leading to cell lysis or release of CD59 into circulation (soluble CD59). This is consistent with the finding that complement deposition is increased on the placental surface in preeclampsia despite increased expression of complement regulators CD55 and CD59 [6,24]. Decreased urinary CD59 concentrations in preeclampsia with severe features may be due to renal impairment or impaired upregulation of CD59 in glomerular endothelial cells, which are more prone to complement mediated effects compared to other organs [25]. For example, urinary C5b-9 levels are markedly increased in women with preeclampsia with severe features, suggesting that CD59 upregulation may be insufficient in the kidney [7,26].

Other mechanisms may also explain CD59 alterations in preeclampsia. The CD59 glycoprotein attaches to host cells via a

Table 3
Plasma and urine CD59 concentrations and correlation with laboratory or clinical measures.

Laboratory or Clinical Measure	Correlation with Plasma CD59 (Spearman's rho)	P*	Correlation with Urine CD59 (Spearman's rho)	P*
Lactate dehydrogenase (U/L)	0.18	0.003	0.02	0.74
Aspartate transaminase (U/L)	0.17	0.005	0.01	0.85
Platelet count (k/μl)	−0.21	<0.001	0.08	0.19
Creatinine (mg/dl)	0.25	<0.001	−0.09	0.17
Urine protein/ creatinine (mg/mg)	0.36	<0.001	−0.07	0.18
Systolic blood pressure (mmHg)	0.28	<0.001	−0.13	0.01
Diastolic blood pressure (mmHg)	0.31	<0.001	−0.14	0.008

*P-value for Spearman's rank correlation coefficient (rho).

glycophosphatidylinositol (GPI) anchor, thus loss of GPI polarity, or alterations in the way GPI-linked proteins are organized on the cell surface, may contribute to altered CD59 expression or function. Such alterations have been demonstrated in pathological conditions such as cancer, infections, and acute inflammatory disorders [27,28]. In pre-eclampsia, it has been shown that the pattern of glycosylation of trophoblastic villi proteins is altered, leading to a change in electrical charge, spatial conformation and mass, which ultimately affects the communication between cells and ligand affinity [29]. Hyperglycemia is another recognized factor that can lead to inactivation of CD59 [30,31]. When glycated, human CD59 loses its ability to inhibit the membrane attack complex (C5b-9), suggesting that pregnant women with hyperglycemia may have greater predisposition to complement mediated vascular damage.

Uncontrolled complement activation leads to widespread tissue damage; therefore, the tight regulation of complement activation is important. In cancer, CD59 may help tumor cells resist treatments that are dependent on complement-dependent cytotoxicity, but inhibition of CD59 can overcome such resistance [32,33]. However, in conditions such as preeclampsia, the actions of CD59 must be strengthened or augmented to minimize complement-mediated destruction of endothelial and trophoblast cells. Our study opens the possibility of investigating the development of therapies that inhibit the formation of C5b-9 or amplify the response of CD59 [8,34]. Future prospective studies should investigate if CD59 in urine or blood could be predictive of preeclampsia with severe features or HELLP syndrome.

We have demonstrated that plasma CD59 concentrations are increased in blood and decreased in urine in association with pre-eclampsia with severe features. Furthermore, increased plasma CD59 concentrations correlated with markers of end-organ injury, including those seen in preeclampsia with severe features and HELLP syndrome. Our data provide further evidence that the complement system is implicated in the pathophysiology of preeclampsia. Soluble CD59 concentrations could be useful in the diagnosis or management of pregnant women with preeclampsia with severe features and may help identify those with altered regulation of terminal complement activation.

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Conflict of interest

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