Preeclampsia with Severe Features, Defining a Subset of Women with Complement-Associated Disease

Richard M. Burwick[1,2,3], Jesús A. Velásquez[3,4,5], Catalina M. Valencia[3,6], Yamile I. Bernal[7], Jaime L. Silva[3,8], Jorge H. Gutiérrez-Marín[3,9], Francisco Edna-Estrada[3,10], Juliana Trujillo-Otálvaro[11], Mónica Rincón[3,12], Jorge E. Tolosa[1,3,5]

1. Oregon Health & Science University, Department of Obstetrics & Gynecology, Portland, OR, 2. Cedars-Sinai Medical Center, , Department of Obstetrics and Gynecology Los Angeles, CA, 3. FUNDARED-MATERNA, Bogotá, Colombia (CO),4. Universidad de Antioquia, Hospital Universitario San Vicente Fundación, Medellin, CO, 5. Universidad de Antioquia, Departamento de Obstetricia y Ginecología; NACER Salud Sexual y Reproductiva, Medellín, CO, 6. Clínica Colsanitas S.A, Bogotá, Colombia, 7. Laboratorio Clínico Sanitas - Clínica Colsanitas S.A.- Grupo de Investigación INPAC, Bogotá, CO, 8. Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, CO, 9. Clínica Universitaria Bolivariana, Universidad Pontificia Bolivariana, Medellin, CO, 10. ESE Clínica de Maternidad Rafael Calvo- Grupo de Investigación Maternidad Segura; Universidad de Cartagena, CO, 11. Hospital General de Medellín Luz Castro de Gutiérrez ESE, Medellin, CO

Abstract #306

Objective: Preeclampsia is heterogeneous. Detection of a universal biomarker may be unrealistic due to distinct pathways of disease. Complement activation, which predisposes to kidney injury, hemolysis and thrombocytopenia, is increased in preeclampsia. We hypothesize that urinary complement biomarker C5b-9, the membrane attack complex, may define a subset of cases with severe, complement-associated disease.

Study Design: Project COPA (COmplement and Preeclampsia in the Americas), an IRB approved, multi-center observational study, enrolled subjects prospectively from 6 centers and 3 cities in Colombia (Bogotá, Cartagena and Medellín (Nov '15-Jul '16). Subjects were enrolled in blocks by gestational age (< or > 34 weeks) and diagnosis (ACOG criteria): 1. healthy; 2. chronic hypertension (CHTN); 3. gestational hypertension (GHTN); 4. preeclampsia (PE) and; 5. PE with severe features (PE-SF). COPA was powered for PE-SF (target, n=100). Clinical data and urine samples were collected by trained coordinators. C5b-9 was measured by enzyme linked immunosorbent assays (Human C5b-9 ELISA, BD Biosciences). For this study, we utilized receiver operating characteristic (ROC) curve analysis, chi-square test and multivariable logistic regression.

Results: 352 subjects were enrolled [healthy (n=59), CHTN (n=42), GHTN (n=92), PE (n=58), PE-SF (n=101)]. Using ROC analysis, we found that urinary C5b-9 has significant diagnostic utility for PE-SF (Figure 1), with area under the curve = 0.74 (0.67-0.80). Urinary C5b-9 level ≥22 ng/ml was the optimal cut-point for PE-SF with 96.4% specificity, positive likelihood ratio 11.3. The odds of PE-SF in those with urinary C5b-9 ≥22 ng/ml was significantly increased, and the association remained strong after adjustment for confounding factors, including total urine protein (Table 1). We found that 40% (41/101) of subjects with PE-SF had urinary C5b-9 levels ≥22 ng/ml, compared to 12% (7/58) of those with PE alone (p<0.001) and 0% (0/134) of those with CHTN or GHTN (p<0.001).

Conclusion: Our data provide strong evidence that a subset of women with preeclampsia with severe features have complement-associated disease, characterized by increased urinary excretion of C5b-9. We propose that women with complement-associated preeclampsia may benefit from targeted complement blockade. Clinical studies are warranted.

Background

- Excess complement activation results in hemolysis, thrombocytopenia and end-organ injury
- Complement activation is increased in preeclampsia
- Complement biomarkers may be used to distinguish a subset of women with complement-associated disease

Research Question

Can urinary levels of C5b-9 be utilized to diagnose PE-SF?

Materials & Methods

Project COPA: **CO**mplement & **P**reeclampsia in the **A**mericas
Design: Multi-center, prospective case-control study
Location: 6 sites in Colombia (Bogotá, Cartagena, Medellín)
Samples: Plasma and Urine; **Measure**: C5b-9 (ELISA)
Enrollment: Blocks by gestational age and diagnosis

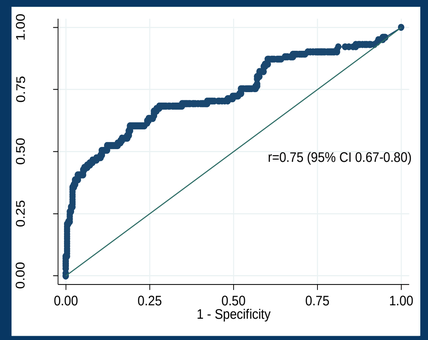
Table 1. Baseline characteristics of study population.

	Healthy n=59	CHTN n=42	GHTN n=92	PE n=58	PE-SF n=101
GA (wks)	34±4.1	34±4.3	36±4.1	35±3.7	33±4.2
Age (yrs)	30±6.3	30±6.4	26±6.2	26±6.8	26±6.5
BMI (kg/m^2)	24±3.9	28±5.5	26±4.6	26±5.0	25±4.3
SBP (mmHg)	116±13	141±12	142±11	141±11	149±17
DBP (mmHg)	68±9.9	86±12	90±10	89±10	95±12

Data are mean ± standard deviation; CHTN, chronic hypertension; GHTN, gestational hypertension; PE, preeclampsia; PE-SF, preeclampsia with severe features; GA, gestational age; SBP, systolic blood pressure; DBP, diastolic blood pressure

Results

Figure 1. ROC curve for diagnosis of PE-SF, utilizing C5b-9 levels in urine.



Optimal cut-point for PE-SF:

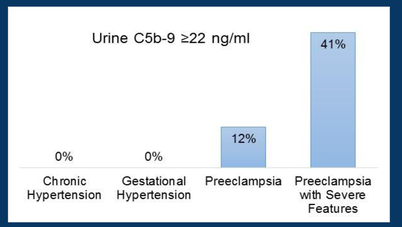
Urinary C5b-9 level **≥22ng/ml**

- 96% specificity
- LR+ 11.3

Table 1. Odds of PE-SF with urine C5b-9 ≥22 ng/ml, by logistic regression.

Variable	PE-SF Odds Ratio	95% CI	p-value
Urine C5b-9 ≥22 ng/ml (unadjusted)	18.4	8.5-39.9	<0.001
Urine C5b-9 ≥22 ng/ml (adjusted for age, BMI, race, parity, gestational age)	16.4	6.9-39.0	<0.001
Urine C5b-9 ≥22 ng/ml (additional adjustment for urine protein and creatinine)	13.1	4.8-36.1	<0.001

Figure 2. Subjects with urine C5b-9 ≥22 ng/ml, stratified by hypertensive disorder



P<0.001, PE-SF vs. CHTN, GHTN or Preeclampsia

Conclusion

- Urine C5b-9 is a useful diagnostic marker for preeclampsia with severe features (PE-SF).
- Urine C5b-9 levels ≥22 ng/ml are associated with 13x greater odds of PE-SF, independent of confounders, and such levels are not seen with CHTN or GHTN.
- A subset of women with PE-SF appear to have complement-associated disease and may benefit from targeted therapy.

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