Increased complement activation in preeclampsia, a strong association with severe disease.

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Abstract #305

Objective: A single unifying cause of preeclampsia may not exist, and distinct pathways should be explored. We sought to investigate the complement pathway, which mediates kidney injury, hemolysis and thrombocytopenia, when activated in excess. We hypothesize that complement activation, assessed by C5b-9, is increased in preeclampsia with severe features.

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, blood and urine were collected by trained coordinators, with C5b-9 measured by enzyme linked immunosorbent assays (Human C5b-9 ELISA, BD Biosciences). Data were analyzed by test of medians, Spearman's correlation and logistic regression.

Results: 352 subjects were enrolled, with baseline characteristics in Table 1. Compared to controls, plasma C5b-9 levels were increased in all subjects with a hypertensive disorder (Figure 1a). In those <34 weeks, plasma C5b-9 levels were only significantly elevated in PE-SF vs controls [median (IQ range), 2974 ng/ml (1622-4308) vs. 1378 ng/ml (1096-2440), p=0.009]. In urine, C5b-9 levels were specifically increased in PE-SF, but not other hypertensive disorders (Figure 1b). Notably, urine C5b-9 differentiated PE-SF from PE without SF (p=0.001). Those with urine C5b-9 levels above the upper quartile (>8.5 ng/ml) had significantly increased odds of PE-SF, even after multivariable adjustment (age, BMI, parity, race, systolic, diastolic blood pressure, and urine protein), [aOR (95% CI), 4.02 (2.05-7.87), p<0.001]. Of clinical importance, the association of urine C5b9 with PE-SF was independent of total urine protein.

Conclusion: In this study, the largest to-date of complement biomarkers in preeclampsia, we describe a strong association between complement activation and severe disease. Increased levels of C5b-9 in plasma and urine may define a distinct pathway to preeclampsia. These findings provide rationale to investigate targeted complement blockade in a clinical trial.

Background

- Preeclampsia is a heterogeneous disorder and there may be distinct subsets of disease
- Complement activation has been proposed as an important pathway of disease in preeclampsia and HELLP syndrome
- In hypertensive disorders of pregnancy, it is not known if complement activation increases with disease severity

Research Question

Is complement activation, assessed by C5b-9 in plasma and urine, increased in preeclampsia with severe features?

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

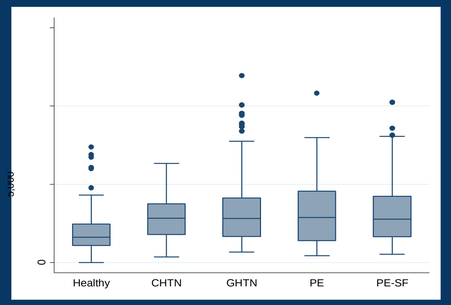
Table 1. Baseline characteristics of study population

	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

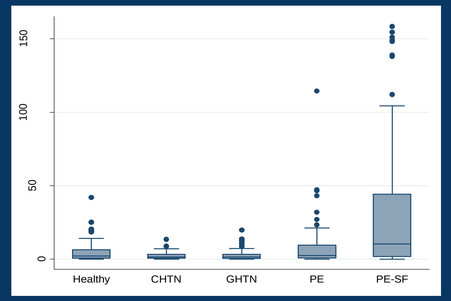
Figure 1a. Plasma C5b-9 levels by study group.



Plasma C5b-9 increased in all hypertensive disorders

p-value (vs. healthy): CHTN (p=0.02); GHTN, PE (p=0.003); PE-SF (<0.001)

Figure 1b. Urine C5b-9 levels by study group.



Urine C5b-9 increased only in PE-SF

P-value (vs. healthy): p=NS (CHTN, GHTN, PE); P<0.001, PE-SF
p-value (vs. PE): p=NS, CHTN, GHTN; p=0.001, PE-SF

Horizontal line, median; box, 25th-75th percentile; whiskers, 10th-90th percentile; dots, outside values; CHTN, chronic hypertension; GHTN, gestational hypertension; PE, preeclampsia; PE-SF, preeclampsia with severe features

Table 2. Urine C5b-9 and odds of PE-SF, logistic regression

Variables	PE-SF (OR)	95% CI	P-value
Urine C5b-9 >8.5 ng/ml (Upper Quartile)	6.8	4.0-11.6	<0.001
Urine C5b-9 >8.5 ng/ml (Adjusted for age, race, parity, BMI)	6.6	3.6-12.0	<0.001
Urine C5b-9 >8.5 ng/ml (Additional adjustment for systolic and diastolic BP, urine protein)	4.0	2.1-7.9	<0.001

Conclusion

- Complement activation is increased in preeclampsia, and there is a strong association with severe disease (PE-SF).
- Plasma C5b-9 is increased in all hypertensive disorders.
- Urine C5b-9 is increased only in PE-SF, independent of clinical factors, blood pressure or urine protein.
- Complement activation is an important pathway in PE-SF and there is rationale to target complement blockade in the setting of a clinical trial.

Collaborations:

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