# Excess complement activation is associated with adverse outcomes in women with hypertensive disorders of pregnancy

Jesús Velásquez[1,2,3], Richard M. Burwick[3,4,5], Catalina M. Valencia[3,6], Johanna Vargas[7], Jaime L. Silva[3,8], Francisco Edna-Estrada[3,9], Jorge H. Gutiérriez-Marín[3,10], Juliana M. Trujillo-Otálvaro[11], Ana M. Gómez[1], Mónica Rincón[3,4], Carlos Cabas[12], Alvaro Quintero[11], Nataly González[13], Viviana Lenis-Ballesteros[1], Jorge E. Tolosa[2,3,4]

1. Universidad de Antioquia, Hospital Universitario San Vicente Fundación, Medellin, Colombia (CO), 2. Universidad de Antioquia, Departamento de Obstetricia y Ginecologia; NACER Salud Sexual y Reproductiva, Medellín, Colombia, 3. FUNDARED-MATERNA, Bogotá, CO,4. Oregon Health & Science University, Department of Obstetrics & Gynecology, Portland, OR, 5. Cedars-Sinai Medical Center, Department of Obstetrics and Gynecology Los Angeles, CA, 6. Clínica Colsanitas S.A, Bogotá, CO, 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. ESE Clínica de Maternidad Rafael Calvo, Grupo de Investigación Maternidad Segura, Cartagena, CO,10. Clínica Universitaria Bolivariana, Universidad Pontificia Bolivariana, Medellin, CO,11. Hospital General de Medellín, Luz Castro de Gutiérrez ESE, Medellin, CO, 12. Universidad del Sinú-ESE Clínica de Maternidad Rafael Calvo, Cartagena, CO,13. Universidad de Cartagena-ESE Clínica de Maternidad Rafael Calvo, Cartagena, CO.

## Abstract #329

**Objective:** Complement activation occurs in normal pregnancy, but excess activation is associated with preeclampsia. Terminal complement activation generates C5b-9, the lytic membrane attack complex, which mediates organ damage. We hypothesize that activation of C5b-9 is increased in women with hypertensive disorders of pregnancy and adverse outcomes

**Study Design:** We assessed urine and plasma C5b-9 levels in hypertensive subjects from project COPA (**CO**mplement and **P**reeclampsia in the **A**mericas), an IRB approved, multi-center observational study, which enrolled subjects from 6 centers and 3 cities in Colombia (Bogotá, Cartagena and Medellín; Nov 15-Jul 16). Hypertensive subjects enrolled in blocks by gestational age ( ≤ or ≥ 34 weeks) and diagnosis (ACOG criteria): 1. chronic hypertension (CHTN); 2. gestational hypertension (GHTN); 3. preeclampsia (PE) and; 4. PE with severe features (PE-SF). COPA was powered for PE-SF (n=100). Clinical data, urine and plasma were collected by trained coordinators, with C5b-9 measured by enzyme linked immunosorbent assays (Human C5b-9 ELISA, BD Biosciences). Maternal and neonatal outcomes were assessed individually and as composite outcomes. Data were analyzed by Chi-square, t-test and logistic regression

**Results:** 293 subjects were evaluated [CHTN (n=42), GHTN (n=92), PE (n=58), PE-SF (n=101)]. Adverse maternal and neonatal outcomes, by plasma C5b-9 quartiles 1-4 (pC5b9, Q1-4), are shown in **Table 1**. Composite maternal outcomes were increased with low pC5b9 (Q1, ≤1443 ng/ml), particularly for those ≥ 34wks (OR 2.93, 95% CI 1.0-8.6, p=0.05). For neonates, preterm birth (PTB) was increased with lower pC5b9 levels (PTB, 2870 ± 1904 vs. term, 3572 ± 2262 ng/ml, p=0.006). Adverse outcomes, by urine C5b-9 (uC5b9) quartiles, are shown in **Table 2**. They were more common with high uC5b9 levels (Q4, ≥8.49 ng/ml), predominantly due to increased kidney injury (OR 3.0, 95%CI 1.1-8.4, p=0.036) and PTB (OR 2.0, 95% CI 1.2-3.5, p=0.01)

**Conclusion:** We describe a novel pattern of complement activation (low plasma / high urine C5b-9), which associates with adverse maternal and neonatal outcomes in women with hypertensive disorders of pregnancy. We postulate that excess complement activation results in kidney injury and depletion of complement factors in plasma, with resultant pregnancy complications.

## Background

- Complement activation occurs in normal pregnancy and it is increased in preeclampsia.
- Terminal complement activation generates C5b-9, which mediates end-organ damage.
- The association between C5b-9 and adverse pregnancy outcomes is unkown

## Research Question

- Is excess complement activation, assessed by C5b-9 in plasma and urine, associated with adverse maternal and neonatal outcomes ?

## 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.

| Characteristic | CHTN n=42 | GHTN n=92 | PE n=58 | PE-SF n=101 |
|---|---|---|---|---|
| GA (wks) | 34±4.3 | 36±4.1 | 35±3.7 | 33±4.2 |
| Age (yrs) | 30±6.4 | 26±6.2 | 26±6.8 | 26±6.5 |
| BMI (kg/m$^2$) | 28±5.5 | 26±4.6 | 26±5.0 | 25±4.3 |
| SBP (mmHg) | 141±12 | 142±11 | 141±11 | 149±17 |
| DBP (mmHg) | 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

**Table 1.** Adverse maternal and neonatal outcomes, stratified by **plasma** C5b-9 quartiles

| | Plasma C5b9 Quartile 1 <1443 ng/ml | Plasma C5b9 Quartile 2 1444-2558 ng/ml | Plasma C5b9 Quartile 3 2559-4074 ng/ml | Plasma C5b9 Quartile 4 >4075 ng/ml |
|---|---|---|---|---|
| **Composite Adverse Maternal Outcome* (%)** | 18.3 | 12.9 | 8.4 | 10.0 |
| **Composite Adverse Neonatal Outcome† (%)** | 55.0 | 54.3 | 38.6 | 40.0 |

**Table 2.** Adverse maternal and neonatal outcomes, stratified by **urine** C5b-9 quartiles

| | Urine C5b9 Quartile 1 <0.69 ng/ml | Urine C5b9 Quartile 2 0.70-2.34 ng/ml | Urine C5b9 Quartile 3 2.35-8.48 ng/ml | Urine C5b9 Quartile 4 >8.49 ng/ml |
|---|---|---|---|---|
| **Composite Adverse Maternal Outcome* (%)** | 8.7 | 7.9 | 13.9 | 17.1 |
| **Composite Adverse Neonatal Outcome† (%)** | 43.5 | 42.1 | 41.7 | 56.6 |

* Composite maternal outcome (any of the following): eclampsia, pulmonary edema, acute kidney injury (Cr ≥1.0 mg/dl) or liver dysfunction (AST/ALT ≥70 U/L)

† Composite neonatal outcome (any of the following): preterm birth <37wks, 5-minute Apgar <7, NICU admission or respiratory distress syndrome

### Key Findings

- Lower plasma C5b-9 levels in preterm vs. term neonates:
  - 2870 ng/ml vs. 3572 ng/ml, p=0.006
- Highest urine C5b-9 levels (Quartile 4) in the following:
  - Preterm birth: OR 2.0, 95% CI 1.2-3.5, p=0.01
  - Acute kidney injury: OR 3.0, 95% CI1.1-8., p=0.036
- Divergent pattern of low plasma C5b-9 and high urine C5b-9 in association with adverse outcomes.

## Conclusion

- A novel pattern of complement activation (low plasma / high urine C5b-9), is associated with adverse outcomes in women with hypertensive disorders of pregnancy.
- Excess complement activation may result in kidney injury and depletion of complement factors in plasma, with resultant pregnancy complications.
- Further clinical studies in a larger cohort are warranted to validate these findings.

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