A functional measure of cell surface-directed complement activity in Systemic Lupus Erythematosus with and without antiphospholipid antibodies during pregnancy

Gloria F. Gerber, Michael A. Cole, Daniel A. Flores, Daniel W. Goldman, Nikhil Ranjan, Shruti Chaturvedi, Michelle A. Petri, Robert A. Brodsky

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Building Interdisciplinary Research Careers in Women's Health

BACKGROUND

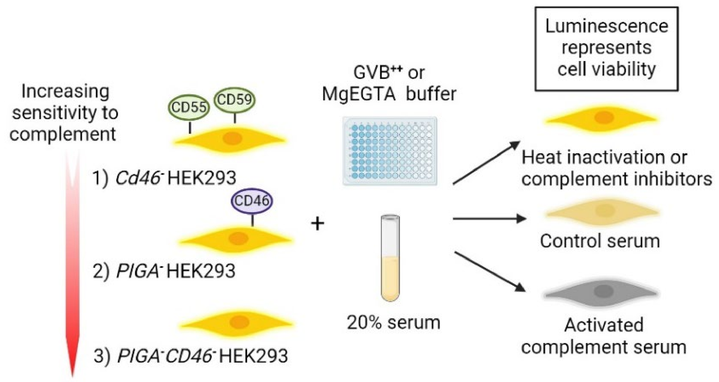
- Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis and/or adverse pregnancy outcomes (APOs) with persistent antiphospholipid antibodies (aPLs) and can occur with Systemic Lupus Erythematosus (SLE).
- Prior studies implicate dysregulation of the complement system in APS-related APOs.
- Complement is part of the innate immune system that is closely linked to coagulation and inflammatory pathways.
- We developed the bioluminescent modified Ham (mHam), a novel *functional* assay of complement activity directed against the cell surface that can identify pathway-specific effects.
- We aimed to define changes in the complement system during pregnancy in women with SLE+APS compared to SLE alone.
- Serum samples collected during pregnancy were obtained from the Hopkins Lupus Biorepository (1999-2013).
- APOs were collected from biorepository dataset.

Table 1. Composite APO

Composite 'Adverse Pregnancy Outcome'
Thromboembolism
CAPS/pregnancy-associated TMA
Preeclampsia, HELLP
Fetal growth restriction
Preterm birth
Fetal death
Neonatal death

METHODS

Figure 2. Bioluminescent Modified Ham



- MCP/CD46 knockout LiveLight HEK293 cells were incubated with 20% patient serum
- The effect of complement on cell metabolic health was measured by serial luminescence
- Relative luminescence was calculated after 1-hour by comparing participant serum to its heat-inactivated sample.
- Positive is defined as <62% relative luminescence

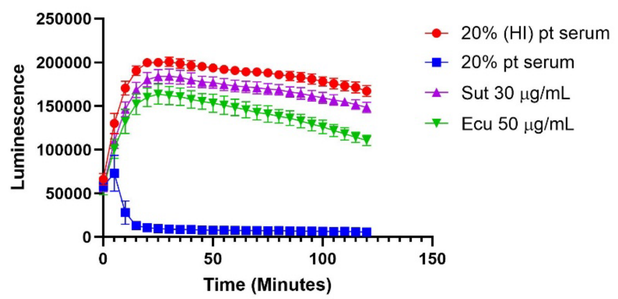


Figure 3. Bioluminescent mHam from woman with APS+SLE, and pregnancy was complicated by preterm birth at 35 weeks. Representative example from first trimester. Complement-mediated cell killing blocked by eculizumab (ecu), sutimlimab (sut; classical pathway inhibitor). (HI) heat inactivation.

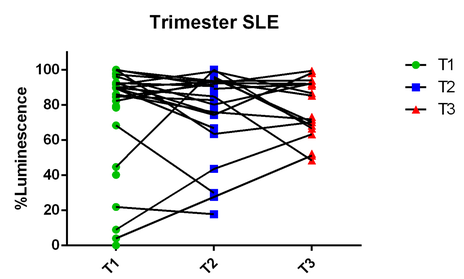


Figure 4. Relative luminescence by trimester. No significant difference in complement activity by trimester was observed.

RESULTS

- All pregnancies resulted in live births
- Pregnancy complications meeting the composite 'APO' occurred in 8/38 pregnancies (1 IUGR, 5 preterm births, and 2 pre-eclampsia)
- 13/73 samples from 9 women with increased complement activity (6/26 first trimester, 4/27 second trimester, 3/20 third trimester samples)
- 3/11 women with APS and 6/26 with SLE (6/20 with (+) aPL, 0/6 with (-) aPL) had positive bioluminescent mHam
- 3/9 (33.3%) women with positive bioluminescent-mHam experienced APOs vs 6/28 (21.4%) (NS).
- Complement activity was blocked by classical and terminal pathway inhibitors

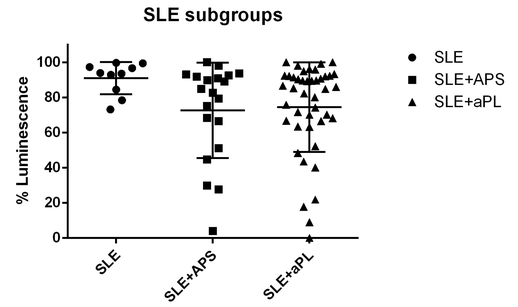
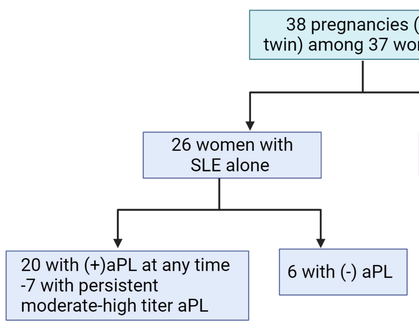
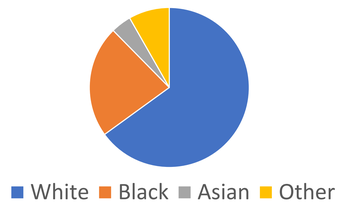


Figure 6. Relative luminescence by aPL/APS positivity. Only women with presence of aPL had increased complement activity.

Figure 1. Study Pregnancies and Demographics





73 total samples

- 26 first trimester, 27 second trimester, 20 third trimester
- 12 pregnancies with 1 sample collected, 14 pregnancies with samples from 2 trimesters, 11 with samples from all trimesters

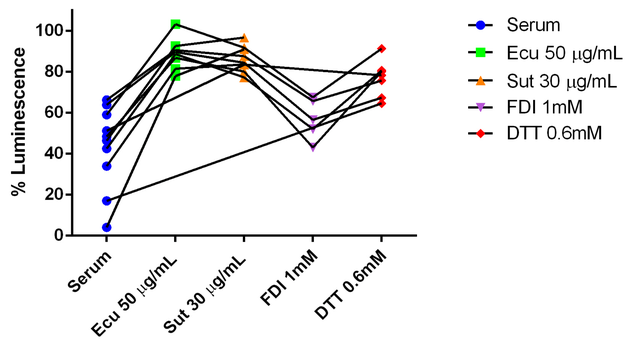


Figure 5. Complement-mediated killing blocked by classical and terminal complement inhibitors.

CONCLUSION

- Women with SLE and aPL/APS demonstrate increased complement activity during pregnancy compared to SLE without aPL
- Limitations include age of the samples and variable processing times, lower than expected rate of APOs, and changing clinical and research definitions of APS and aPL positivity
- Larger, prospective studies are needed

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