onset of nephritis). The urine protein/creatinine ratio is 1100 mg/gm, down from 3700 mg at onset of nephritis and stable over the last year. She is not in a relationship now but wants to preserve her ability to have biological children in the future and she is very concerned that she will develop recurrent nephritis. She has decided she would like to freeze her eggs and asks your opinion.

a. aPL (LAC, aCL, ab2GPI) are all negative

b. aPL are 'triple positive', with high levels of LAC, aCL and ab2GPI

Discussion Point

- The best way to assess and guide a patient with SLE who is planning oocyte cryopreservation, in the setting of negative and positive aPL

Learning Objectives

- Explain the importance of safe and effective contraception for women with SLE at risk for unintended pregnancy and be able to assess patients and recommend the best options for them
- Describe the risks of ovarian stimulation for patients with SLE, with and without aPL, and suggest and discuss specific management options with the reproductive endocrinologist

Case 3: 36-year-old female seeking pregnancy counselling
Rebecca Fischer-Betz

Maggy is a 36-year-old female office assistant with 8-year history of systemic lupus erythematosus (SLE). Past manifestations of SLE included polyarthritis, pleuritis, positive ANA and dsDNA antibodies and low complement. She had been initially treated with corticosteroids and hydroxychloroquine. Two years ago she had a flare with polyarthritis and treatment with methotrexate was added. Currently she is feeling well. She asks about the possibility of a pregnancy. Her menstruation is regular and has had no previous pregnancies.

Laboratory tests revealed Hb 12,8 g/dl; Plt 233 K/µl; leucocytes 3.800/µl; Anti-dsDNA 122 (< 80 IU/ml), complement is normal. She is presently taking methotrexate 12.5 mg sc/week and hydroxychloroquine 200 mg/day.

Discussion Points

- Performing pregnancy counselling in women with SLE
- Treatment options available prior to conception and during pregnancy

Case 4: 29-year-old female with lupus nephritis
Rebecca Fischer-Betz

Sara is a 29-year old female from Sri Lanka living with her husband in Germany for five years. She was diagnosed with SLE about one year ago based on the presence of fever, fatigue, leukopenia, positive antinuclear antibodies, positive anti-dsDNA and low complement. In addition, she had proteinuria (>5 g/24 hours) and abnormalities of urinary sediment. A renal biopsy showed Class IV proliferative lupus nephritis. She was initially treated with prednisolone and cyclophosphamide (Euro Lupus protocol) followed by mycophenolate mofetil. She had an early abortion 3 years ago (unplanned pregnancy). Her menstruation cycle has been irregular since she stopped taking an estrogen-containing pill after diagnosis. She worries about infertility. She currently reports joint pain and fatigue, she sleeps a lot. Her physical examination is unremarkable, no arthritis, no edema, blood pressure 125/85 mmHg. Laboratory tests reveal Hb 10,8 (12–16 g/dl) g/dl, creatinine 1,1 (<0,9) mg/dl, urinalysis 40 RBC, Pr/Cr 2,1 g/g, anti-dsDNA 433 (<80 IU/ml), complement C3 66 (90–180 mg/dl), C4 <6 (10–40 mg/dl). Antiphospholipid-antibodies are negative. She is presently taking prednisone 10 mg, mycophenolate mofetil 2 g/day, ramipril 5 mg/day and furosemide 20 mg. Her older brother is also suffering from lupus nephritis. He has stopped immunosuppressive treatment several months ago and is doing well.

Discussion Point

- When and how to plan pregnancy in a patient with lupus nephritis

Learning Objectives

- Demonstrate knowledge of the influence of SLE on pregnancy and vice versa
- Describe main predictors of pregnancy complications in women with SLE
- Describe currently accepted management of SLE prior to conception and during pregnancy
- Explain the importance of pregnancy counselling in SLE patients

Hot topics: the role of complement in SLE

23 COMPLEMENT IN SLE

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10.1136/lupus-2021-la.23

The complement system and systemic lupus erythematosus (SLE) have been intertwined for nearly 70 years. Complement consumption secondary to increased turnover was an early salient observation. Autoantibodies to nuclear materials forming immune complexes were likely mediating tissue damage. A second and fascinating observation was that a complete deficiency of C1q, C4 or C2 predisposed to SLE. These two key findings have been the heart of lupus-related complement research over the next 50 years.

Complement as a biomarker A major more recent goal here has been to explore complement's activating fragments; namely, fluid phase split products and cell-bound complement activation products (CB-CAPS). The hope here was to provide more sensitive and specific biomarkers to monitor disease activity. A thorough review of these data was recently published.[1] While both split products and CB-CAPS show promise, there remain issues in demonstrating clinical superiority to standard serum C4 and C3. Limitations that commonly arise relate to the complex methodology, availability and interpretation.

Complement in etiopathogenesis The underlying hypothesis has been that complement is required for the proper handling of nuclear debris and thereby prevent an inappropriate autoimmune response. This arena remains a work in progress, but several informative studies have recently been published:[2–5] In my comments, I will highlight several issues: A) the deficiency story; B) C3b instructing how the opsonic material is processed; C) Evidence that the C4A gene regulates autoreactive B cells in murine lupus; D) C4A gene as a major player in sex-biased vulnerability in SLE; and E) Discovery of an intracellular complement system.

Complement therapeutics Rare genetic variants in complement regulators have been identified in aHUS and C3G and successfully treated with anti-C5 mAbs. This therapeutic development

along with the discovery of rare variants in age-related macular degeneration have ignited the field of complement therapeutics.

Learning Objectives

- Describe the long history of the complement system's interactions with lupus for the lupologist
- Advances in defining the role of 'complement' as a biomarker for lupus
- Discuss recent advances understanding how complement deficiency predisposes to SLE

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24 THE ROLE OF COMPLEMENT AND COMPLEMENT INHIBITION IN APS PREGNANCY

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10.1136/lupus-2021-la.24

Women with antiphospholipid syndrome (APS) are at increased risk for adverse pregnancy outcomes, including preeclampsia, fetal and neonatal death and fetal growth restriction. Studies in mice implicate inflammation, particularly complement activation, as an essential and causative factor in placental insufficiency, fetal loss and growth restriction.[1] Complement activation is initiated by classical, alternative and lectin pathways. The convergence of the three pathways on C3 results in generation of common effectors: anaphylatoxins, opsonins and the membrane attack complex. Mice deficient in alternative and classical pathway complement components (factor B, C4, C3 and C5) and mice treated with inhibitors of complement activation (anti-C5 mAb, anti-factor B mAb, C5a receptor antagonist peptide) are resistant to fetal injury induced by aPL,[1] indicating that both pathways contribute to damage. Similarly, pregnancies in hypertensive mice prone to preeclampsia are rescued with inhibitors of complement activation.[2] Studies in humans support the role of complement in aPL-associated pregnancy complications and in preeclampsia and growth restriction in non-autoimmune women.[3] Complement fragment C4d, a marker of classical pathway activation, is present in placentae from women with systemic lupus erythematosus (SLE) and/or APS and from women with preeclampsia. Mild hypocomplementemia has also been reported in primary APS. The presence of loss of function variants in complement regulatory proteins in patients with preeclampsia with SLE and/or aPL antibodies or without autoimmunity links complement activation to disease pathogenesis.[4] Furthermore, in prospective studies of SLE and/or APL-positive patients and in non-autoimmune patients, elevated levels of the complement activation products in blood, particularly factor Bb, were associated with adverse pregnancy outcomes.[5] Taken together, these findings suggest a role for complement inhibition for the prevention of APS-triggered placental insufficiency in high risk pregnancies.

Learning Objectives

- Explain the risk factors for adverse pregnancy outcomes in APS
- Describe the mediators and mechanism of pregnancy complications in patients in APS
- Describe potential targets to treat and prevent pregnancy complications in patients with APS

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25 THE INTERFACE OF COMPLEMENT AND COAGULATION PATHWAYS

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10.1136/lupus-2021-la.25

The most menacing challenge to survival faced by organisms throughout the animal kingdom is injury accompanied by invasion of foreign pathogens. To survive these threats, organisms have developed effective means to contain wounds by simultaneously and coordinately limiting bleeding with clot formation, restricting and fighting infections, while facilitating rapid initiation of healing. This finely tuned, synchronized activation of coagulation and complement – the latter, a major component of innate immunity – supports the notion that common molecular mechanisms regulate these multi-protein, blood-borne cascade systems, and that dysregulation of either, may negatively impact on both, causing disease.

The last couple of decades has seen major progress in identifying cellular and molecular links between the complement and coagulation systems, yielding diagnostic insights and strategies for the design of innovative therapies. We and others have delineated mechanisms by which complement activation promotes coagulation.[1] For example, the complement-mediated anaphylatoxin C5a, triggers activation of endothelial cells, platelets and monocytes, and upregulates the coagulation initiator, tissue factor (TF). The lytic membrane attack complex (C5b-9), generated terminally by activation of complement, also induces TF expression, while the complement lectin pathway serine proteases (MASPs) directly activate clotting factors. Notably, the key coagulation-induced clotting protease, thrombin,[2] feeds back and amplifies complement activation, thereby sustaining a vicious, escalating cycle, that may result in profound damage to the host.

The physiologic relevance of the interplay between coagulation and complement is evident in many metabolic, malignant, inflammatory, infectious (e.g. COVID-19),[3] thrombotic