Illustrative Cases of Kidney Disease Unique to Women

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CASE 1: OVARIAN FAILURE FROM CYCLOPHOSPHAMIDE

Courtesy of Dr. Iru Chen, University Hospital in Taiwan

A 37-year-old Vietnamese woman with a history of biopsy-proven antineutrophil cytoplasmic autoantibody–associated vasculitis presented with a 24-hour total protein of 7.1 g, and serum creatinine of 1.7 mg/dL. She was treated aggressively with intravenous pulse methylprednisolone, plasmapheresis, and oral cyclophosphamide 50 mg twice daily for the next 6 months; afterward she was switched to mycophenolate mofetil 1,000 mg twice daily. Her serum creatinine peaked at 2.19 mg/dL five months after presentation, but returned to 1.39 mg/dL 10 months later. Her serum albumin also increased from 2.7 to 3.8 g/dL during this period. Her urine protein-to-creatinine ratio decreased to 626 mg/g. Although her renal condition improved, her menses became irregular by five months after the initiation of cyclophosphamide, eventually stopping altogether.

Teaching Points

There are several reasons why the patient may be experiencing abnormal or absent menses. First of all, the presence of chronic kidney disease itself can disturb the hypothalamic-pituitary axis, which will result in abnormal ovulation.[1] However, in this case, it is likely that the use of cyclophosphamide, which is a gonadotoxic agent, caused the irreversible premature ovarian failure. The incidence of premature ovarian failure with cyclophosphamide is associated with the cumulative dose and sharply increases with the patient's age.[2] She would have been 32 at the time she received cyclophosphamide, and the reported rate of ovarian failure in her age group exceeds 50%.[2] Interestingly, oral administration causes sustained amenorrhea more so than intravenous formulations.[3] There is mixed data regarding the potential benefit of gonadotropin-releasing hormone analogs for fertility preservation in women receiving cyclophosphamide, with two meta-analyses showing benefit[4,5] and another demonstrating no benefit of gonadotropin-releasing hormone analog co-treatment,[6] but this should be considered in women who desire children, and cannot be safely treated with alternative immunosuppressive options that do not cause ovarian damage (e.g., rituximab or mycophenolate mofetil). We recommend that this patient be referred to a fertility specialist to confirm the diagnosis of premature ovarian failure, and if confirmed, she will likely need an egg donor for a future pregnancy.

CASE 2: LUPUS IN PREGNANCY

Courtesy of Dr. Liz Lightsone, Imperial College London

A 34-year-old Sri Lankan woman with systemic lupus, diagnosed 10 years prior to presentation with joint pain and treated with steroids, presented with nephrotic-range proteinuria, a serum albumin of 2.0 g/dL, and a serum creatinine of 1.25 mg/dL. Kidney biopsy revealed class IV lupus nephritis. The patient was given rituximab (RITUXILUP [Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis] regimen) and achieved complete remission by 9 months, with urine protein-to-creatinine ratio down to 34 mg/g, serum albumin of 3.3 g/dL, and a serum creatinine of 0.78 mg/dL. The patient was interested in pregnancy, and the plan was to initiate azathioprine after 18 months in remission and allow her to proceed, but she presented with an unplanned pregnancy neither on maintenance immunosuppression nor taking hydroxychloroquine. In the first trimester, she developed systemic symptoms, including rash, arthralgias, and alopecia along with nephrotic syndrome, with a serum albumin of 1.0 g/dL, urine protein of 10 g/day, edema, and hypertension. Her serum creatinine increased from 0.56 to 0.90 mg/dL, and serology supported a significant flare of lupus nephritis. She was given steroids, azathioprine, and tacrolimus. She was hospitalized for nephrotic syndrome at 19 weeks for 3 to 4 weeks for control of her nephrotic state, including the initiation of low-molecular-weight heparin to prevent thrombosis. She was then seen twice weekly for the rest of her pregnancy. Her edema, serology, and serum creatinine improved. Her proteinuria, though improved, remained in the nephrotic range. Her prednisone dosage was subsequently tapered down to 10 mg once daily, and at 37 weeks, she delivered a female infant weighing 2470 g. The patient was switched from azathioprine to mycophenolate mofetil postpartum.

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Teaching Points

Even in patients with a history of significant lupus nephritis prior to pregnancy, reasonable pregnancy outcomes can be expected so long as patients enter pregnancy well prepared in a solid remission on pregnancy-safe immunosuppression. Further, all women with lupus should be on hydroxychloroquine, and this can be started in pregnancy as it has been shown to maintain remission, whereas discontinuation during pregnancy has been reported to promote lupus flares and result in higher prednisone exposure.[7–9] The recently published PROMISSE (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus) study is informative as it excluded women with active nephritis or active systemic disease; the women were followed in specialist centers and nearly all were on hydroxychloroquine.[10] Overall, 81% of 236 women had uncomplicated pregnancies. However, should women flare in pregnancy, there are treatment options. In general, the first-line approach would be steroids: pulses of high-dose methylprednisolone can be given for rapid effect with oral prednisolone at 0.5 mg/kg/d with the aim to taper as rapidly as tolerated.[11] Azathioprine, up to 2 mg/kg/d, along with calcineurin inhibitors are frequently used alone or in combination as steroid-sparing agents.[12] Additionally, women with significant proteinuria should have prophylactic low-molecular-weight heparin to reduce the risk of venous thromboembolism.

CASE 3: DIABETIC NEPHROPATHY AND PREGNANCY

Courtesy of Dr. Michelle A. Hladunewich, University of Toronto

A 29-year-old woman with a long-standing history of type 1 diabetes mellitus presented at 8 weeks' gestation. She had known retinopathy, gastroparesis, and diabetic nephropathy with a baseline creatinine of 1.44 mg/dL and 1.5 g of urine protein. Throughout pregnancy her proteinuria increased, eventually into the nephrotic range (9.2 g/d), and her creatinine further deteriorated to 1.72 mg/dL. She developed anasarca and visual loss. Her baby was born at 31 weeks' gestation weighing 3 pounds and 6 ounces. Unfortunately, she was lost to follow-up in the postpartum period and returned again pregnant with twins 2 years later. Her creatinine was now 1.92 mg/dL and she had 3.2 g of proteinuria. She rapidly progressed to end-stage renal disease again with severe nephrosis (urine protein 13 g/d) despite pregnancy termination for severe volume overload and cardiac compromise.

Teaching Points

Poorly controlled diabetic nephropathy is associated with very poor pregnancy outcomes. Proteinuria invariably worsens and often significantly,[13] and women with more advanced renal dysfunction will progress.[14] Prepregnancy optimization and postpartum care are critical. In addition to meticulous management of blood glucose levels and stabilization of retinopathy, blood pressure control and treatment of proteinuria with blockade of the renin-angiotensin-aldosterone system likely improve outcomes.[15–17] Uncontrolled studies, wherein blood glucose targets were met along with renin-angiotensin-aldosterone system blockade to lower proteinuria maintained until conception, noted less of the expected rise in urine protein along with stable renal function during postpartum follow-up.[16,17] The use of these agents needs to be carefully discussed with prospective parents because of the risks of teratogenicity with exposure beyond the first trimester.[18] Reinstitution of renin-angiotensin-aldosterone system blockade postpartum is compatible with breast-feeding and again should be employed as soon as possible in the postpartum period to slow renal progression.[19–21] Of the angiotensin-converting enzyme inhibitors, enalapril, captopril, and quinapril have the lowest concentrations in breastmilk and thus are deemed to be safe.

CASE 4: ADVANCED CHRONIC KIDNEY DISEASE PROGRESSING TO END-STAGE RENAL DISEASE IN PREGNANCY

Courtesy of Dr. Michelle A. Hladunewich, University of Toronto

A 20-year-old woman was referred at 12 weeks' gestation with stage 5 chronic kidney disease (CKD; eGFR 10 mL/min/1.73 m^2). She was born with a solitary kidney. She had multiple episodes of urinary tract infections in her childhood, including an episode of severe pyelonephritis complicated by acute kidney injury and subsequently chronic renal impairment. She was already receiving modality education and planning to start hemodialysis when pregnancy was diagnosed. During her first visit, she complained of anorexia, nausea, and vomiting as well as fatigue with a decrease in her functional capacity. On physical examination, her blood pressure was 110/79, and her heart rate was 84 beats per minute. Her jugular venous pulsation was 2 cm above the sternal angle. Auscultation of her heart and lungs were normal. Routine laboratory investigations included a creatinine of 4.67 mg/dL with a blood urea nitrogen of 56.8 mg/dL, potassium of 5.2 mEq/L, and a serum bicarbonate of 18 mEq/L. On the abdominal ultrasonogram, her right (solitary) kidney measured 8 cm in length with a thin cortex and increased echogenicity of the corticomedullary junction.

After counseling her on the maternal and fetal risks related to her advanced kidney disease, and discussion of her management, she decided to carry on with her pregnancy. She also agreed to initiate renal replacement