Pregnancy outcomes in a patient with Sjögren's disease with renal involvement

Abhishek Joshi¹, Keelin O'Donoghue², Uzma Mahmood²,
Debasish Banerjee³ and Anita Banerjee¹

Abstract

Background: Maternal and fetal outcome in pregnancy with renal failure is unpredictable, where each condition can adversely affect the other. We present a case of steroid sensitive Sjögren's nephritis worsened by pregnancy, demonstrated over the course of multiple pregnancies and investigated the aetiology.

Case: A 28-year-old nullipara with a diagnosis of primary Sjögren's syndrome presented with a deterioration of renal function. A diagnosis of secondary tubulo-interstitial nephritis was made on renal biopsy. Her first pregnancy ended in the second trimester with a decision to deliver a female infant at 27 weeks due to worsening maternal renal function. Renal function improved immediately. A second pregnancy ended in a first trimester miscarriage. The third and fourth pregnancies delivered male infants at 35 and 34 weeks, with worsening renal function in each pregnancy, reaching end stage. Repeat biopsy showed extensive glomerulosclerosis and male cells were identified.

Conclusions: This case of Sjögren's syndrome with renal disease demonstrated the increased risk of fetal and maternal adverse pregnancy outcomes. Renal function worsened in each pregnancy and progressed to end-stage renal disease. Fetal microchimerism offers an interesting mechanism for our patient's renal failure and its apparent relationship to her pregnancies.

Keywords

Maternal-fetal medicine, nephrology, rheumatology, immunology

Case presentation

A 28-year-old nulliparous lady presented with a tender goitre. Ultrasound revealed no pathology, but thyroid stimulating hormone (TSH) was raised (65.78 mIU/L [0.10–10 mIU/L]). A provisional diagnosis of Hashimoto's thyroiditis was made. Immunological testing found a positive anti-nuclear antibodies, positive Rheumatoid factor, positive perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and positive SSA (5.9 IU/mL) and SSB (4.5 IU/mL). Labial and salivary gland biopsy showed lymphoplasmacytic infiltration, confirming a diagnosis of primary Sjögren's syndrome with sialadenitis.

Renal involvement

After two years of follow-up, renal function tests showed a rise in creatinine from 1.13 mg/dL (100 µmol/L) to 2.03 mg/dL (180 µmol/L) within 12 months. Renal ultrasound found bilateral, 10 cm kidneys. A 24-h urine collection demonstrated normal urinary electrolytes and proteinuria of 0.32 g/24 h [normal range <0.08 g/24 h]. Renal biopsy found lymphocytic infiltrate in the tubules and interstitium, and normal glomeruli to both light and electron microscopy. Immunostaining was negative, including C3. A diagnosis of tubulo-interstitial nephritis (TIN) was made.

Immunosuppressive therapy was initiated with prednisolone, which remained difficult to wean despite the introduction of mycophenolate mofetil (MMF).

First pregnancy

She conceived when her creatinine was 1.55 mg/dL (137 µmol/L). Creatinine began to rise in spite of an increase in prednisolone dose throughout the second trimester, peaking at 2.16 mg/dL (187 µmol/L) when a decision was made to deliver the fetus at 26⁺6 weeks gestation due to rapidly deteriorating maternal renal function. A live 435 g baby girl was delivered by Caesarean section and required intensive care management. Maternal renal impairment improved immediately after delivery.

Further pregnancies

Further attempts to wean immunosuppression were unsuccessful. A pregnancy three years later ended in a first trimester spontaneous miscarriage. She conceived again shortly after this with a creatinine at 1.58 mg/dL (140 µmol/L) which had increased by 30% by the second trimester. She delivered a 1.940 kg baby boy at 36 weeks gestation by elective Caesarean section; APGAR score 1 min 9; 5 min 10. Her creatinine had climbed to 2.10 mg/dL (186 µmol/L) despite being managed with high-dose prednisolone. Serum creatinine returned to a baseline of 1.70 mg/dL (150 µmol/L) again soon after delivery.

Her third pregnancy took a similar course, with conception when creatinine was 1.70 mg/dL (150 µmol/L), and delivery of a healthy baby boy weighing 2.114 kg, APGAR score 1 min 9; 5 min 10 at 36 weeks by elective Caesarean section, when the creatinine reached 2.60 mg/dL (230 µmol/L). However, creatinine did not return to baseline after this delivery and has progressively worsened. Figure 1 shows creatinine results across all three pregnancies.

A repeat biopsy showed extensive glomerulosclerosis. XY fluorescence in-situ hybridisation (XY-FISH) and Y-FISH analysis detected male cells in the renal parenchyma (Figure 2). Her background renal disease was considered irreversible and she was prepared for renal replacement therapy.

¹Department of Acute Medicine, Princess Royal University Hospital, South London Healthcare Trust, London, UK

²Anu Research Centre, Department of Obstetrics and Gynaecology, University College Cork, Cork, Republic of Ireland

³Department of Nephrology, St George's Healthcare Trust, London, UK

Corresponding author:

Anita Banerjee, Obstetric Physician, Department of Acute Medicine, Princess Royal University Hospital, South London Healthcare Trust, London, UK.

Email: a.banerjee@nhs.net

Figure 1. Renal function through three pregnancies in a patient with Sjögren’s nephritis. Graphs showing serum creatinine and prednisolone dose through the weeks of three separate pregnancies in the same patient.

Figure 2. Renal biopsy demonstrating fetal microchimerism in a patient with Sjögren's nephritis. Slides A and B show XY-FISH of the renal biopsy. Male cells were identified in the kidney biopsy. An X chromosome is labelled with SpectrumOrange and a Y chromosome labelled with SpectrumGreen. Slides C and D show Y-FISH analysis of female cells. Y chromosomes are seen labelled SpectrumOrange.

Discussion

Our case of Sjögren's syndrome with renal involvement demonstrates the increased risk of fetal and maternal adverse pregnancy outcomes. We suggest a hypothesis for the cause of complications in pregnancies with Sjögren's syndrome, and its adverse effect on renal function.

Renal impairment is a common complication of Sjögren's syndrome. A large, retrospective study found that renal impairment was present in 33.5% of patients with Sjögren's disease,¹ although the prevalence of renal disease in Sjögren's appears to vary geographically.² TIN is the most common biopsy finding.³

Literature discussing the effects of pregnancy on systemic manifestations of Sjögren's disease is sparse. One report describes acute mesangioproliferative glomerulonephritis presenting during pregnancy in a patient with Sjögren's, resulting in end-stage renal failure.⁴ This is the first case to describe a worsening TIN, over the course of three consecutive pregnancies.

As disease onset is typically later than the reproductive years, retrospective studies predominate. A number of studies with varying methodologies have failed to demonstrate a reduction in fertility or increase in the risk of complications of pregnancy in women with Sjögren's syndrome,⁵⁻⁸ none of these studies differentiated between Sjögren's patients with or without renal impairment.

The presence of fetal cells in mothers, persisting for long periods after pregnancy is called fetal microchimerism (FMC).⁹ The predilection for females and the yearly increase in the incidence of autoimmune diseases, combined with their similarity to iatrogenic graft-versus-host diseases has directed investigation of potential causative links between FMC and maternal autoimmune diseases. A large, retrospective cohort study ($n=1,035,639$) found more diagnoses of autoimmune disease in the first year after Caesarean section and vaginal delivery when compared to abortion.¹⁰

Despite the attractions of this theoretical link, evidence to support microchimerism as the cause of Sjögren's has been mixed. Research has focussed on correlating the presence of non-maternal deoxyribonucleic acid (DNA) in mothers with Sjögren's syndrome with disease activity or progression. All the studies have been small, and largely focused on patients with Sjögren's disease who have had male offspring. Polymerase chain reaction (PCR) or FISH have been used to detect male DNA in the mother. XY-FISH analysis of our patient's recent renal biopsy demonstrates the presence of male cells in the renal parenchyma.

A PCR-based study of peripheral blood samples using the DZY1 gene as a marker found evidence of FMC in patients with Sjögren's disease, but these findings were not significantly different from healthy women.¹¹ Further studies using PCR assays of varying sensitivity for the male SRY1 gene all returned negative results in peripheral blood samples from patient suffering from Sjögren's syndrome.¹²⁻¹⁴

PCR and FISH analysis of inflammatory lesions have yielded mixed results. Three small, SRY1 PCR studies (sample sizes between 6 and 16) of salivary glands in Sjögren's syndrome found no evidence of male DNA in these glands.¹⁴⁻¹⁶ However, the largest study, with 56 patients suffering from both primary and secondary Sjögren's disease, found that, whilst PCR of peripheral blood samples for SRY1 were negative in all cases, PCR for SRY1 was positive in the labial salivary glands of 10 of 28 Sjögren's patients, and in none of the 10 control patients.¹⁷ The same study demonstrated the presence of male cells in the inflammatory lesions using FISH, linking the presence of male cells to target organ damage in Sjögren's. Ours is the first confirmation of FMC in the kidney of a patient with Sjögren's nephritis.

There appears to be good evidence that microchimerism does not occur in the peripheral blood of Sjögren's patients, while evidence supports FMC playing a role in the inflammatory lesions of Sjögren's syndrome.

These studies do not distinguish between primary and secondary Sjögren's syndrome, nor do they give information about the severity of disease in their patient populations. Finally, the mere presence of microchimeric cells does not directly implicate these cells in the pathogenesis of Sjögren's disease.

Conclusion

We present the first case of steroid sensitive Sjögren's nephritis worsened by consecutive pregnancies. We provide evidence of FMC in the renal biopsy of the case. FMC offers an interesting pathophysiological mechanism to explain our patient's renal failure and its apparent relationship to her pregnancies.

References

- Lin DF, Yan SM, Zhao Y, et al. Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome. *Chin Med J (Engl)* 2010; 123: 3252-3257.
- Kaufman I, Schwartz D, Caspi D, et al. Sjögren's syndrome – not just Sicca: renal involvement in Sjögren's syndrome. *Scand J Rheumatol* 2008; 37: 213-218.
- Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjögren's syndrome: a clinicopathologic study. *Clin J Am Soc Nephrol* 2009; 4: 1423-1431.
- Adam FU, Torun D, Bolat F, et al. Acute renal failure due to mesangial proliferative glomerulonephritis in a pregnant woman with primary Sjögren's syndrome. *Clin Rheumatol* 2006; 25: 75-79.
- Haga HJ, Gjesdal CG, Koksvik HS, et al. Pregnancy outcome in patients with primary Sjögren's syndrome: a case-control study. *J Rheumatol* 2005; 32: 1734-1736.
- Mavragani CP, Dafni UG, Tzioufas AG, et al. Pregnancy outcome and anti-Ro/SSA in autoimmune diseases: a retrospective cohort study. *Br J Rheumatol* 1998; 37: 740-745.

7. Julkunen H, Kaaja R, Kurki P, et al. Fetal outcome in women with primary Sjögren's syndrome. A retrospective case-control study. *Clin Exp Rheumatol* 1995; 13: 65–71.
8. Brucato A, Doria A, Frassi M, et al. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. *Lupus* 2002; 11: 716–721.
9. Fugazzola L, Cirello V and Beck-Peccoz P. Fetal microchimerism as an explanation of disease. *Nat Rev Endocrinol* 2011; 7: 89–97.
10. Khashan AS, Kenny LC, Laursen TM, et al. Pregnancy and the risk of autoimmune disease. *PLoS One* 2011; 6: e19658.
11. Miyashita Y, Ono M, Ueki H, et al. Y chromosome microchimerism in rheumatic autoimmune disease. *Ann Rheum Dis* 2000; 59: 655–656.
12. Mijares-Boeckh-Behrens T, Selva-O'Callaghan A, Solans-Laqué R, et al. Fetal microchimerism in Sjögren's syndrome. *Ann Rheum Dis* 2001; 60: 897–898.
13. Toda I, Kuwana M, Tsubota K, et al. Lack of evidence for an increased microchimerism in the circulation of patients with Sjögren's syndrome. *Ann Rheum Dis* 2001; 60: 248–253.
14. Endo Y, Negishi I and Ishikawa O. Possible contribution of microchimerism to the pathogenesis of Sjögren's syndrome. *Rheumatology (Oxford)* 2002; 41: 490–495.
15. Aractingi S, Sibilia J, Meignin V, et al. Presence of microchimerism in labial salivary glands in systemic sclerosis but not in Sjögren's syndrome. *Arthritis Rheum* 2002; 46: 1039–1043.
16. Carlucci F, Priori R, Alessandri C, et al. Y chromosome microchimerism in Sjögren's syndrome. *Ann Rheum Dis* 2001; 60: 1078–1079.
17. Kuroki M, Okayama A, Nakamura S, et al. Detection of maternal-fetal microchimerism in the inflammatory lesions of patients with Sjögren's syndrome. *Ann Rheum Dis* 2002; 61: 1041–1046.