Successful outcome of pregnancy in patients with anti-neutrophil cytoplasm antibody–associated small vessel vasculitis

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Pregnancy in patients with anti-neutrophil cytoplasm antibody–associated vasculitis is reportedly associated with a high risk of fetal and maternal complications. Here we describe the outcome of pregnancies in patients with granulomatosis with polyangiitis and microscopic polyangiitis at five centers in the United Kingdom using a retrospective case review of all women who became pregnant following diagnosis. We report 15 pregnancies in 13 women resulting in 15 live births including one twin pregnancy and 13 singleton pregnancies. One patient had an unplanned pregnancy and a first trimester miscarriage while taking methotrexate. All other pregnancies were planned following a minimum of 6 months clinical remission. Eleven successful pregnancies were delivered vaginally at full term, whereas three were delivered by cesarean section. All infants were healthy with no neonatal complications on their initial health check within the first 24 h of delivery and no evidence of neonatal vasculitis. One relapse occurred during pregnancy and was successfully treated with an increased dose of azathioprine and corticosteroids, intravenous immunoglobulin, and plasma exchange therapy. One patient developed tracheal crusting and subglottic stenosis of infective etiology in the third trimester requiring tracheal debridement post delivery. No patient had a relapse in the first 12 months postpartum. Thus, successful pregnancy outcomes can occur following planned pregnancy in women in sustained remission on non-teratogenic therapies.

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There are limited data on the outcomes of pregnancy in patients with anti-neutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV): microscopic polyangiitis and granulomatosis with polyangiitis (formerly Wegener's granulomatosis). Despite the rarity of these diseases and the peak age at onset being 65–75 years, pregnancy is increasingly common in this population of patients, a result of the improvement in therapies and survival.[1] Pre-pregnancy counseling is challenging because of the paucity of data regarding pregnancy outcomes and a lack of evidence to guide the management of disease relapse in these patients. What data are available are based largely on case reports or small retrospective case series that report frequent complications such as pre-term births,[1–4] premature rupture of membranes,[5] first trimester miscarriage,[5] and relapse of disease resulting in fetal and maternal death.[1–5] Recent reports have suggested more favorable outcomes[6] with a lower risk of disease relapse but still a high incidence of pregnancy loss and pre-term births.[5,7] We predicted that planned pregnancies in women in sustained clinical remission, maintained on non-teratogenic treatments, would lead to more favorable pregnancy outcomes than those previously reported. Here we report the outcomes of pregnancy in women with AAV at five centers in the United Kingdom.

RESULTS

Patient characteristics and diagnosis

Fifteen pregnancies were observed in 11 women with granulomatosis with polyangiitis and two women with microscopic polyangiitis, resulting in 15 live births. One woman had a first trimester miscarriage following an unplanned pregnancy while taking methotrexate (patient 5), and one woman had a dizygotic twin pregnancy (patient 3). The median age at diagnosis was 25 years (range 15–33 years). All women were of white ethnicity. Organ involvement and disease severity at presentation are shown in Table 1. The median Birmingham Vasculitis Activity Score (BVAS) at diagnosis was 12 (range 4–19). ANCA indirect

Table 1 | Main characteristics of the 13 AAV patients prior to pregnancy

Patient no.	Age	Dx	Organs involved	ANCA IIF pattern	ELISA specifity and titer (units/ml)	Treatment before pregnancy	Cumulative CYC (g)	Relapse prior to pregnancy and organ system affected	Disease-free remission prior to pregnancy (months)
1	33	GPA	Lung; ENT	cANCA	PR3 22.1	RTX; Pred; MTX	0	1 yr ENT	6
2	20	GPA	ENT; Skin; Kidney	cANCA	PR3 26.5	Pred; MTX	13	7 yrs Skin, Renal	72
3	28	GPA	Pituitary; Kidney	cANCA	PR3 15.2	Pred; AZA	18.5	none	18
4	15	GPA	Lung; ENT	cANCA	PR3 31.5	Pred; AZA	10.5	6 yrs Lung, Renal	65
5	22	GPA	Lung; ENT	cANCA	PR3 45.5	Pred; MTX	9.5	none	14
6	33	GPA	ENT	cANCA	PR3 3.5	Pred; AZA	0	none	40
7	24	GPA	Lungs; ENT; Kidney; CNS	cANCA	PR3 15.3	Pred; AZA MMF; MTX	8.5	none	6
8	19	MPA	Kidney; Lung	pANCA	MPO 11.0	Pred; Plasma exchange; AZA	36	6 yrs ENT, Renal	68
9	29	GPA	ENT	pANCA	MPO 2.5	Pred; AZA	6	9 yrs Renal	102
10	25	GPA	ENT; Lung; MSK	pANCA	Neg	Pred; CIC; AZA	10	none	18
11	17	MPA	Lung	pANCA	MPO 1.8	Plasma exchange; MMF; AZA	12	6 yrs Skin, Renal	60
12	29	GPA	ENT; Lung	cANCA	PR3 >1000	Pred; MMF	8.5	4 yrs Renal 3 yrs Renal	31
13	25	GPA	Joints; skin; GI; ENT; PNS	Neg		Pred; AZA	15	4 yrs Lung, Renal	42

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibody; AZA, azathioprine; CIC, ciclosporin; CNS, central nervous system; CYC, cyclophosphamide; Dx, diagnosis; ELISA, enzyme linked immunosorbance assay; ENT, ear, nose, and throat; GI, gastrointestinal; GPA, granulomatosis with polyangiitis; IIF, indirect immunofluorescence; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MSK, musculoskeletal; MTX, methotrexate; Neg, negative; No., number; PNS, peripheral nervous system; PR3, proteinase 3; Pred, prednisolone; RTX, rituximab; Yrs, years.

immunofluorescence pattern and enzyme linked immunosorbance assay specificity and titer at diagnosis are shown in Table 1. The number and nature of relapses and the interval between relapse and conception are outlined in Table 1.

Treatment (induction, maintenance, and preconception therapy)

Eleven patients received corticosteroids and cyclophosphamide (CYC) therapy for induction of remission (median cumulative dose 10 g (range 6.0–36 g). One patient received CYC and steroids with additional plasma exchange for life-threatening pulmonary hemorrhage. One patient received four weekly rituximab infusions (375 mg/m^2 body surface area).

In patients with planned pregnancies, methotrexate and mycophenolate mofetil were discontinued in favor of safer alternatives (azathioprine and steroids) at least 6 months prior to planned pregnancy. The median duration between CYC treatment and first pregnancy was 68 months (range 32–216 months). One patient with localized upper respiratory tract involvement had immunosuppression discontinued prior to conception (patient 6). Maintenance therapy at the time of conception is shown in Table 2. Patients taking cotrimoxazole as an anti-Staphylococcus agent were switched to erythromycin, with the exception of one patient who, following discontinuation of cotrimoxazole preconception, developed worsening nasal crusting. Cotrimoxazole was therefore restarted, and symptoms resolved prior to conception. Fiberoptic endoscopic examination around the time of conception showed normal nasal and sinus compartments after restarting cotrimoxazole, which was continued during pregnancy (patient 10).

Conception and pregnancy

The median age at first pregnancy was 34 years (range 26–40 years). Two women required assisted conception. One woman with secondary ovarian failure underwent infertility treatment with ovum donation, *in vitro* fertilization, and successful uterine implantation (patient 3). A second woman without evidence of ovarian failure but with difficulty in conceiving was treated with *in vitro* fertilization only (patient 10). The median time between diagnosis and conception of first pregnancy was 4 years (range 3–20). The median disease-free period prior to pregnancy was 24 months (range 6–78; Table 1).

All women were in clinical remission (BVAS = 0) at the time of conception: 11 women for at least 12 months, one woman for 6 months, and one woman had low-grade crusting rhinitis that resolved 3 months prior to conception (patient 10). The median Vasculitis Damage Index (VDI) score was 2 (range 0–3) at the time of conception. No patient had detectable proteinuria defined as urine albumin to creatine ratio >2.5 mg/mmol. All patients had blood presure $<140/80$ mm Hg without anti-hypertensive treatment, except patient 8 who had well-controlled hypertension on amlodipine. The patient was switched to labetalol and methyldopa in pregnancy. Renal function is shown in Table 2. Five (36.5%) women had an estimated glomerular filtration rate (eGFR) <90 ml/min per 1.73 m^2 at the time of conception (Table 2).

ANCA detection at conception and during pregnancy

ANCA indirect immunofluorescence patterns and enzyme linked immunosorbance assay specificities and titers during pregnancy are shown in Table 2. Five patients were ANCA positive by indirect immunofluorescence at conception but