Pregnancy in granulomatous vasculitis

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Abstract

Objective—To study the fetal and maternal outcome of pregnancy in patients with granulomatous vasculitis.

Methods—Four pregnancies in two patients with Wegener's granulomatosis (WG) and one patient with Churg-Strauss syndrome (CSS) were identified and followed in our specialised clinic for pregnancy and connective tissue diseases.

Results—Three pregnancies ended with live babies and one with intrauterine death at 25 weeks of gestation. One WG patient remained in remission throughout pregnancy and the other experienced severe activity at 12 weeks. The CSS patient was in remission during her first pregnancy, but the disease flared severely in the second.

Conclusions—Pregnancy in patients with granulomatous vasculitis requires pre-conceptual planning, careful clinical management, and vigorous treatment of active disease.

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Pregnancy has rarely been reported in patients with Wegener's granulomatosis (WG) and Churg-Strauss syndrome (CSS), partly because their peak incidence occurs at a later age (fourth and fifth decades); in addition, there is a preponderance of male patients.¹ We describe two pregnancies in two patients with WG and two pregnancies in one patient with CSS, and discuss the management of pregnancy in these vasculitic syndromes.

Case reports

PATIENT 1

A 29 year old housewife who had a two year history of sinusitis developed severe headache during her second pregnancy. Six weeks after the birth of a healthy baby girl, she developed a sore throat, arthralgia, painful itchy ears, and sinusitis. Subsequently, she suddenly noticed a widespread urticarial rash and deterioration of her persistent headache. Despite a trial of 10 mg of prednisolone, she did not improve and had to be admitted to hospital. On admission, she had fever, sweats, nasal bleeds, a tender neck, persistent headache, slight fullness over the right maxillary sinus, and painful ankles. The diagnosis of probable limited WG was made on clinical grounds as a nasal biopsy specimen provided insufficient tissue for assessment and the antineutrophil cytoplasmic antibody (ANCA) test was negative. Her

erythrocyte sedimentation rate (ESR) was 87 mm/1st h and neutrophil count $12.8 \times 10^9/l$. Antinuclear (ANA), extractable nuclear antigen (ENA), and double stranded (ds) DNA antibodies were all negative. Rheumatoid factor was weakly positive. There was no clinical or biochemical evidence of renal involvement. Her sinus radiograph showed soft tissue shadowing over the lateral part of the right maxillary antrum. Chest radiograph was normal. Orbital computed tomography (CT) scan showed that the right and left middle turbinate bones had irregular outline and were surrounded by a soft tissue density which was presumed to be a Wegener's granuloma. Two pulses of 500 mg of cyclophosphamide were given one week apart, followed by 100 mg daily oral azathioprine and 10 mg of oral prednisolone. In the following three years, she had three mild flares, related to a reduction of the steroid dose. She became pregnant again, during a remission period, on no medication. The course of this third pregnancy was satisfactory, without any need for immunosuppressive treatment. She had a normal delivery with a birth of a healthy baby boy of 3174 g at 40 weeks of gestation. Four months later, she started to experience dizziness, tinnitus, collapse, and left sided ear and facial pain.

The ANCA test remained negative. ESR, renal, and liver function tests were normal at this time. These symptoms remitted spontaneously and one year later, at the time this paper was written, she was pregnant again, of 32 weeks gestation; although she presented nasal stuffiness, no systemic treatment was required.

PATIENT 2

A 24 year old accounts clerk started to experience generalised malaise, fever, sweats, loss of 5 kg of weight, left ear discharge, and nasal congestion. A nasal biopsy specimen was obtained and was suggestive of WG. She was treated with oral prednisolone 25 mg daily. Subsequently, when she was first seen in St Thomas's Hospital, she developed cough, pleuritic chest pain, and muscle aches. Her chest radiograph showed two ill defined cavitating opacities in the left mid zone. Sinus radiograph showed no abnormalities. c-ANCA was positive, while ANA, ENA, and dsDNA antibodies were negative. ESR was 36 mm/1st h and a leucocytosis of $14.4 \times 10^9/l$ was noted. During this admission, the prednisolone was kept at the same dose and intravenous pulses of 500 mg of cyclophosphamide were introduced as described previously.² After a total of six pulses over four months complete

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remission occurred. The dose of prednisolone was reduced progressively to 5 mg during this period. Before the planned seventh pulse, the patient developed a small vasculitic lesion on her right hand and an effusion of the right knee. In addition, there was a recurrence of cough. ESR was 119 mm/1st h and the white cell count was $13.3 \times 10^9/l$. The ANCA test was persistently positive and her renal function tests remained normal. Before cyclophosphamide had been administered it was found that the patient was pregnant, with a gestation of 12 weeks. The dose of prednisolone was increased to 25 mg, but she refused to take azathioprine. In the subsequent weeks she had a good clinical response to prednisolone therapy with remission of the vasculitic lesions, but with persistent leucocytosis, and ANCA remaining positive. The dose of prednisolone was reduced progressively to 15 mg. When she was about 25 weeks pregnant, she had a stillbirth of a macerated fetus. There was no clinical recurrence in the postnatal period, but, immediately after the delivery, the pulses of intravenous cyclophosphamide were reintroduced and the dose of prednisolone was reduced to 10 mg.

PATIENT 3

A 24 year old secretary presented with anorexia, fever, diarrhoea, and generalised malaise. She reported a weight loss of 15 kg over the preceding three months, diffuse pains and numbness in arms and legs, and weakness of the left hand. She subsequently observed an urticarial rash which she had noticed occasionally in the past. She had suffered from asthma since childhood and had a history of excision of two nasal polyps five months earlier. On examination, she was severely ill, with deformities suggesting a severe widespread mononeuritis multiplex affecting the hands and feet, and generalised muscle wasting and weakness. Her blood count showed an eosinophilia of 9%, ESR 20 mm/1st h, and the liver and renal function tests were normal. ANA, dsDNA, and ENA antibodies were negative. c-ANCA was negative, but p-ANCA was weakly positive. Chest and sinus radiographs were normal. Electrophysiological assessment confirmed a pattern consistent with mononeuritis multiplex. A diagnosis of CSS was made and the patient was treated with three pulses of 1 g of methylprednisolone, followed by three pulses of 500 mg of cyclophosphamide at one week intervals. She made a rapid recovery on this regimen, the oral steroids were reduced gradually, and she commenced taking azathioprine 100 mg daily one month later. For the following two years, she recovered the neurological deficits and was clinically in remission, apart from a slightly stuffy nose. She was maintained on oral azathioprine 150 mg and prednisolone 5–15 mg.

During this period of remission, the patient became pregnant for the first time. Azathioprine and prednisolone were maintained throughout pregnancy. She had an uneventful

pregnancy without obstetric or medical complications, but reported a worsening of the stuffiness in her nose in the last four weeks of pregnancy. Her eosinophil count was normal and the ANCA test was persistently negative. She had a vaginal delivery at 40 weeks gestation and delivered a healthy baby boy weighing 3459 g. She stopped azathioprine after the delivery in order to breast feed and the prednisolone was kept at 10 mg daily. Four months later, when her treatment was 5 mg of prednisolone daily, she became pregnant again. However, at 10 weeks of gestation she reported an itchy skin rash, asthma, blocked sinuses, and tingling pain in her arms and legs. She increased the steroid dose to 15 mg daily, but the symptoms persisted. At 21 weeks gestation, when she was seen for the first time in this pregnancy, she had signs of mononeuritis multiplex and asthma. She commenced 100 mg of azathioprine. ANCA was negative. Her ESR and renal function tests were normal. Her clinical condition improved and at 39 weeks gestation she delivered a healthy baby girl weighing 3180 g. For the second time, she stopped the azathioprine to breast feed and continued to receive 5 mg of prednisolone. Six weeks later, she had a flare of the disease with asthma, sinus involvement, and a marked rash. The symptoms were controlled after azathioprine was recommenced.

Discussion

Diagnosis and clinical monitoring of vasculitis may be difficult in pregnancy. In the literature, 15 pregnancies have been described in 10 patients with WG.^{3–5} Among these, the disease was diagnosed during gestation in four mothers, and in the postpartum period in three, while eight pregnancies occurred in known cases of the disease. Although our first patient presented few laboratory alterations and no renal involvement, we believe that her clinical and radiological manifestations and her prompt response to treatment supported a possible diagnosis of limited WG. She started to have activity in the postpartum of her second pregnancy, when the diagnosis was made. Our second mother with WG had her disease diagnosed less than one year before the first gestation.

In WG, it seems that flares may occur at any time in relation to gestation, not being concentrated in any trimester, and perhaps having a tendency to occur in the puerperium. Regarding the 15 cases described in the literature, among the nine women who presented activity during pregnancy, two pregnancies ended in therapeutic abortion, at seven and 10 weeks of gestation, and a spontaneous early miscarriage preceded maternal death in one case. Another maternal and fetal death occurred at 21 weeks. In contrast, the three women who were in remission during pregnancy had normal babies. Our first patient, who was in remission during her first pregnancy after the diagnosis of WG, delivered a healthy baby. The second

patient presented a severe flare of disease at 12 weeks and ended the pregnancy with a stillbirth. Fetal outcome may, therefore, be related to maternal disease activity.

Our patient with known CSS experienced little disease activity in her first pregnancy, but flared severely in the second, and had further activity during the puerperium. Notably, her disease was controlled with azathioprine, but flared when it was withdrawn, subsiding again when it was reintroduced. Debby *et al*⁶ reported a pregnancy in a patient who had CSS diagnosed one year earlier. She had a severe flare at 24 weeks of gestation, but responded well to steroid therapy. The pregnancy ended successfully with a healthy baby. A second report of CSS apparently starting in pregnancy is documented:⁷ a healthy infant was born, but the mother had two subsequent early miscarriages coincident with exacerbation of her disease; her fourth pregnancy ended in maternal death at seven weeks of gestation after a severe vasculitic flare including fulminant cardiac disease. CSS appears to show a pattern similar to that of WG in pregnancy, with flare being possibly related to delivery or miscarriage. Active disease may lead to fetal demise and maternal death.

With the frequency and grave consequences of flare, it is important to adopt an aggressive approach to treatment of vasculitis in pregnancy. Despite reports of corticosteroids causing cleft palate in rabbits and mice, such congenital abnormalities are extremely rare in humans.⁸ Prednisolone is metabolised in the placenta and its administration in relatively high doses appears to be safe. There are no definite cases of attributable teratogenicity in man. Azathioprine has been widely used in pregnancy after transplantation, in inflammatory bowel and dermatological diseases, and in systemic lupus erythematosus.⁹⁻¹¹ There is a concern whether azathioprine could be responsible for intrauterine growth retardation.¹¹ Although teratogenic in animals, the drug has not been associated with congenital defects in humans; sporadic anomalies have been reported, but these were not believed to be related to the drug therapy.¹² An analysis of 40 pregnancies in SLE patients treated with corticosteroids and azathioprine showed no increased risk of congenital malformations.¹³ Our patient with CSS had active disease during both her pregnancies, which appeared to be very sensitive to azathioprine. No signs of malformation were observed.

Cyclophosphamide has well recognised effects on human female fertility and fetal development, especially in relation to first trimester exposure.^{11, 14} One of our patients was exposed to a low dose of intravenous cyclophosphamide (500 mg) around the time of her early pregnancy, although no fetal ill effect was apparent. It is now our policy to give contraception advice in vasculitic patients

receiving cytotoxic drugs. It is also essential to test women in their childbearing years for pregnancy before administration of pulses of these agents. It would seem prudent to choose prednisolone as the primary agent for treating vasculitis in pregnancy. In severe cases, azathioprine could be added. When nasal stuffiness and sinusitis are troublesome, aqueous beclomethasone spray and oral antibiotics to treat any element of bacterial superinfection may be helpful.

Azathioprine has been detected in human milk only in small amounts, but cyclophosphamide in substantial concentrations.⁸ In our opinion, as there is still controversy in the literature,¹⁵ breast feeding should be avoided when cytotoxic agents are used.

In conclusion, pregnancy should be contemplated with extreme caution in patients with WG and CSS; preferably the mother should be in remission, and active disease should be treated vigorously. The possibility of disease presentation in pregnancy, although extremely rare, must be borne in mind in view of the potentially severe consequences.

NOTE ADDED IN PROOF: Patient 1 subsequently had a normal delivery of a healthy male infant (3.74 kg) at 39 weeks of gestation. The mother reported a slight increase in asthma and sinus pain within two weeks of delivery.

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