Pregnancy complicating Wegener's granulomatosis

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Summary: Pregnancy associated with Wegener's granulomatosis is rare. Therapeutic options are limited. There is a paucity of published literature to guide clinical decision-making in these complex patients. Two cases are presented. Firstly, a 33-year-old woman with generalized Wegener's in remission and off all medications presented with a flare in the third trimester with haemoptysis, raised C-reactive protein and c-anti-neutrophilic cytoplasmic antibody (c-ANCA) levels. Her care was complicated by florid steroid-induced psychosis. With deteriorating disease control, she was treated with pulsed-intravenous cyclophosphamide with a good response. She delivered a healthy baby at 38 weeks. She had a severe postpartum flare. Secondly, a 37-year-old woman with limited Wegener's in remission for the last two years and off all treatment became pregnant after pre-conception counselling. A normal baby was delivered at term. An exhaustive review of all published literature on Wegener's activity in pregnancy is presented along with therapeutic options and recommendations.

Keywords: Wegener's granulomatosis, pregnancy, haemoptysis, cyclophosphamide, steroid-induced psychosis

INTRODUCTION

Wegener's granulomatosis is a rare condition with an annual incidence of 30.4 per million. In the past, multi-organ complications were common making pregnancy unlikely. Literature is scarce regarding its management in pregnancy. As more effective therapies for inducing and maintaining remission emerge, more patients will fall pregnant and the management of Wegener's in pregnancy will become increasingly important.

CASE HISTORIES

Patient 1

A 33-year-old woman with a background of generalized biopsy-proven Wegener's involving her kidneys, lungs and skin presented at 26 weeks. Four years prior, induction therapy with intravenous (IV) cyclophosphamide and methylprednisolone was complicated by psychosis necessitating a prolonged admission. Remission was maintained with mycophenolate mofetil, then methotrexate. Methotrexate was discontinued prior to pregnancy when her disease was in remission. The patient's initial symptoms were fatigue, arthralgia and haemoptysis (C-reactive protein 62 mg/dL, c-anti-neutrophilic cytoplasmic antibody [c-ANCA] positive and proteinase [PR-3] 15 U/mL – normal <5 U/mL). Urine sediment was normal. Prednisone 20 mg was commenced with good response. After five days, the patient became floridly psychotic necessitating cessation of steroids. Psychosis settled three days later, but the Wegener's immediately relapsed with worsening haemoptysis, arthritis and rash. High-resolution

computed tomography scan showed alveolar haemorrhage, which was confirmed on bronchoscopy. IV cyclophosphamide at 0.7 g/m² without steroids was commenced. A response was achieved with a reduction in haemoptysis and improvement in arthritis. Three pulses were given. At 38 weeks, labour was induced and a healthy infant was delivered vaginally. A further pulse of IV cyclophosphamide was given prior to discharge.

Five weeks later, the patient developed severe pulmonary haemorrhage, arthralgia and mouth ulcers (c-ANCA positive and PR-3 >250 AU/mL – normal <20 AU/mL). She was treated with 1 g/m² of cyclophosphamide. Pending response to cyclophosphamide, plasmapheresis (5 cycles of plasma exchange with 4 L albumin 4%) was commenced. The active Wegener's was slow to remit with worsening pulmonary haemorrhage, epistaxis, venous thromboses developing at line sites, mucocutaneous disease and arthritis. IV gammaglobulin, four doses of rituximab 375 mg/m² weekly (with evidence of peripheral B-cell depletion on blood tests) and further pulses of cyclophosphamide were given with little effect. IV methylprednisolone was eventually given with olanzapine cover and sedation in the intensive care unit. The patient's disease eventually settled. Recovery was complicated by sepsis as a result of her immunosuppression. A renal biopsy done because of worsening renal function and profuse red cells in her urine showed florid crescentic glomerulonephritis with 20% scarring, despite the absence of any other features of Wegener's activity, and a negative c-ANCA towards discharge.

Patient 2

A 37-year-old woman with limited Wegener's (on nasal biopsy with positive c-ANCA) was previously treated with methotrexate and prednisone. Pregnancy was planned after disease remission of more than two years (c-ANCA negative and

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PR-3 0 U/mL – normal <5 U/mL) and off all medications. Conception was achieved without difficulty after pre-pregnancy counselling. The patient was closely monitored for disease activity, but remained in remission throughout pregnancy. A healthy infant was delivered vaginally at term. Both mother and infant remain well.

DISCUSSION

ANCA-related vasculitis is a predominantly Th2-mediated response that can be exacerbated by pregnancy. Flares of Wegener's during pregnancy tend to run a more aggressive disease course.^{1,2} Management is further complicated by limited therapeutic options. Published literature is sparse and the lack of evidence-based guidelines makes individual clinical decision-making challenging. To date, there are only 43 pregnancies with Wegener's described. We reviewed all cases of Wegener's in pregnancy published in English from 1970 to date. The English abstracts of the three foreign language case reports were reviewed.^{3–5} The pregnancies were divided into three groups: those with inactive Wegener's at early pregnancy; those with active disease at conception or flared early on; and those who had their Wegener's diagnosed during the current pregnancy (Figure 1). Some patients had more than one pregnancy. Twin deliveries were considered as one pregnancy outcome.

Stable or inactive disease at conception

Twenty-two pregnancies occurred in patients with Wegener's with stable disease. Eight flared during pregnancy.^{6–10} The median time to flare was 19.5 weeks. All patients had respiratory involvement. At least half the patients who flared were maintained on azathioprine.^{6–8} One patient whose flare necessitated the use of cyclophosphamide had a therapeutic abortion.⁸

More than half who remained in remission throughout pregnancy were maintained on oral steroids.^{1,5,11–16} While there was improved fetal maturity in this group, maternal complications were more common. Two developed gestational diabetes and four developed preeclampsia or hypertension^{11,12,15} during the pregnancy.

Active disease at conception or early pregnancy

Seven patients with previously diagnosed Wegener's with persistent disease activity during conception or early pregnancy have been reported.^{1,3,14,17–19} While most had respiratory involvement (limited Wegener's), only three had generalized Wegener's with renal involvement.^{3,14,17} The patients were treated with a variety of immunosuppressants. Two patients were given cyclophosphamide in early pregnancy, one had a therapeutic abortion and the other had a miscarriage at 25 weeks.^{1,19} One patient who had disease activity from four weeks and was treated with steroids alone had a miscarriage at 22 weeks and a postpartum flare.¹⁸

Those with active disease at early pregnancy had the worst outcome. More than half of the pregnancies ended in either therapeutic abortions or miscarriages.^{1,3,18,19} There was one case of maternal death from a severe postpartum flare following therapeutic abortion.³ Those who fared the best had been treated with cyclophosphamide after the first trimester or had received additional immunosuppression other than steroids alone.^{14,17,19} Postpartum flares were more common in this group with three of the seven patients affected.^{3,18,19}

Wegener's diagnosed during pregnancy

Thirteen cases of Wegener's presented for the first time during pregnancy.^{2,4,20–30} The median time of presentation was 19.5 weeks. All involved the respiratory system.

Figure 1 Summary of all published case reports in literature according to disease activity during pregnancy

Cyclophosphamide was the most commonly used drug for induction of remission. In all but one patient,²³ cyclophosphamide was used after the first trimester.^{2,24,26,29} No adverse fetal outcomes were documented other than prematurity. Two therapeutic abortions occurred in this group as florid maternal disease necessitated the immediate commencement of cyclophosphamide.^{23,25} The third fetal death in this group occurred *in utero* at 25 weeks when the mother died from an intracerebral bleed.²¹ The patient was treated with azathioprine alone. The recommendation to avoid azathioprine use as monotherapy for treatment of flares during pregnancy is based on this case report and another case where maternal demise occurred during a severe postpartum flare.³

Live births occurred in 61.5% of the pregnancies. Preterm delivery was most common in this group (median gestation of 33.5 weeks).

Wegener's presenting in the puerperium

Four cases of Wegener's that presented in the puerperium have been published.^{1,6,25,31} All mothers were asymptomatic during pregnancy. Two subsequently went on to conceive when their Wegener's was in remission.^{1,6}

Therapeutic options for treatment of flares of Wegener's during pregnancy

The mainstay for induction of remission in Wegener's is a combination of steroids and cyclophosphamide.

Steroid-induced psychosis is rare, but can further compromise therapeutic response despite use of multiple potent immunosuppressive agents as it did in Patient 1. Steroid-induced psychosis in pregnancy poses a risk to the patient and her unborn child.

Cyclophosphamide is a class D drug in pregnancy and a teratogen, yet it remains the best studied chemotherapeutic agent. Aviles³² found cyclophosphamide a safe drug if used after the first trimester. It was associated with a 7% rate of fetal growth restriction and transient cytopenias after birth. There were no congenital abnormalities.^{24,32} While long-term risk to the unborn fetus remains unclear, long-term follow-up of 62 offspring in mothers who had chemotherapy during pregnancy (a large number received cyclophosphamide) is reassuring. The offspring of this cohort were found to be normal physically and neurologically; moreover, school performance and intelligence testing did not differ significantly from controls. They had a normal tolerance to infections and had normal secondary sexual development.³³ While the evidence is by no means conclusive, we believe that cyclophosphamide use should not be withheld in pregnancy if there is life-threatening disease.

Azathioprine, with its well-established safety profile in pregnancy, is useful for the maintenance of remission. It should not be used as monotherapy for the treatment of flares in pregnancy.^{7,26} There have been two cases of fetal loss and one maternal death because of clinical deterioration on azathioprine alone.^{8,21} The two postpartum flares with one maternal death were in patients treated with azathioprine in the antepartum period.^{3,19}

Cotrimoxazole, despite its role as a folate antagonist, has been found to be safe in pregnancy.³⁴ It is useful for maintaining remission in non-pregnant patients with limited disease. It has not been used to successfully maintain disease remission in a pregnant patient.¹⁷ However, it should be considered as prophylaxis for pneumocystis in patients receiving cyclophosphamide.

IV immunoglobulin has been used to treat four patients with active Wegener's during pregnancy. It was well tolerated with no adverse fetal outcomes and appears to be effective.^{7,14,27,30}

Plasmapheresis was used as an emergency adjunct in Patient 1 pending response to cyclophosphamide. The intention was rapid removal of autoantibodies by plasma exchange. Plasmapheresis is rarely used in pregnancy, hence the small literature base.^{7,35-38} Effects of plasmapheresis include rapid shifts of fluid that can precipitate arrhythmias cardiac arrest or pulmonary oedema, sepsis from invasive lines, depletion of anti-thrombin III and other clotting factors can cause coagulopathies.³⁹ Hence, plasmapheresis is used as a last resort.

Rituximab appears to be an emerging therapy for Wegener's. Its safety profile in pregnancy is yet to be determined. Inhibition of neonatal B-cell development remains a concern.⁴⁰

The use of ANCA or PR-3 titres to formulate therapeutic decisions remains controversial.⁴¹⁻⁴³ A small subset of patients with Wegener's may never exhibit any positive ANCA titres.⁴⁴ Studies have demonstrated a discordance between ANCA titres and disease activity.⁴⁵ At this time, we do not have enough evidence to advocate adjustment of therapeutic decisions based on ANCA titres without clinical correlation.⁴⁶

CONCLUSION

From currently available published cases, 65% of Wegener's will flare during pregnancy. The risk is only 35% when the disease has been in remission. However, the occurrence of flares in Wegener's is unpredictable and is not related to the duration of treatment, current maintenance therapy or severity of initial disease.^{8,11,18,23}

Pregnancy outcomes with active Wegener's at conception or early first trimester seemed worse with 57% fetal losses (as opposed to only 23% overall) and one case of maternal death.

The majority of the flares during pregnancy have been of the limited form. Despite the absence of renal involvement, most authors advocate the use of cyclophosphamide.^{2,7} Patients who were treated with immunosuppressants and corticosteroids did better,^{8,13,18,25} than those on steroids alone.^{1,3,8,11,18} There are seven cases where Wegener's has flared postpartum.^{1,3,13,18,19,28} Most flares occur within six weeks of delivery or termination of pregnancy as our first patient did.

The most common fetal complication of Wegener's in pregnancy was prematurity at the median gestational age of 35 weeks.

Details on pregnancy-related complications were not available in all cases. All cases of gestational diabetes, preeclampsia or hypertension occurred in patients taking steroids. Only one fetal anomaly was noted, though this was not related to either disease activity or the drugs used as the patient was off all medications and the disease was in remission.¹¹ Fetal demise from miscarriages or therapeutic abortions was high at 23%. There were two documented maternal deaths: one occurred during pregnancy from active disease treated only with azathioprine and the second occurred a month after termination of pregnancy from a severe postpartum flare.^{3,21}

There is limited information in the literature on the management of Wegener's in pregnancy to guide those caring for these complex patients. A publication bias is likely. The rarity of this clinical situation means that randomized controlled trials are unlikely. This review attempts to bring together the small literature base of Wegener's in pregnancy and our unique method of viewing the individual cases or small cases series by disease activity during early pregnancy has lead us to formulate these recommendations:

- (1) Patients will need to alert their attending physician of their desire to become pregnant so that appropriate pre-conception counselling can be arranged. Pregnancy should only be planned when the disease is in remission. Patients with active disease at conception or in early pregnancy have a very high risk of miscarriage;
- (2) It is impossible to predict flares of Wegener's in pregnancy. Flares will likely involve the respiratory system;
- (3) Even when there is 'limited' Wegener's with the absence of renal involvement, the use of cyclophosphamide use is advocated;
- (4) There are good data to support the safe use of cyclophosphamide in pregnancy after the first trimester;
- (5) In patients with stable disease on maintenance corticosteroids, vigilance regarding gestational diabetes and pre-eclampsia is essential;
- (6) Severe postpartum flares can occur within six weeks after delivery or termination.

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