

## Case report

# Wegener's granulomatosis occurring *de novo* during pregnancy

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### ABSTRACT

*Wegener's granulomatosis (WG) is rarely diagnosed during the reproductive years and uncommonly manifests for the first time during pregnancy. We report a case of de novo WG presenting at 30 weeks gestation with classical symptoms of WG (ENT, pulmonary). The diagnosis was confirmed by radiological, laboratory, and histological investigations. With a multidisciplinary approach, she had a successful vaginal delivery of a healthy baby. She was treated successfully by a combination of steroids, azathioprine and intravenous immunoglobulin in the active phase of disease for induction of remission and by azathioprine and steroids for maintenance of remission. The significant improvement in her symptoms allowed us to continue her pregnancy to 37 weeks when delivery was electively induced. Transplacental transmission of PR3-ANCA occurred but the neonate remained well. This case of de novo WG during pregnancy highlights the seriousness of this disease and the challenge in management of such patients.*

### Case report

A 33-year-old woman presented with a 6-8 week history of sinusitis, deafness, epistaxis, nasal crusting, cough, haemoptysis, myalgias, arthritis particularly affecting hands, knees and feet, skin rash, proteinuria, and haematuria. She was 30 weeks pregnant in her second pregnancy. The pregnancy had been uncomplicated, except for a threatened miscarriage at 6-7 weeks gestation. Foetal growth was normal by ultrasound assessment. She had no significant past medical history. Examination revealed her to be unwell, blood pressure: 100/60 mmHg, pulse: 100/minute regular, bi-basal crackles were audible in the chest. She had swelling of the metacarpophalangeal joint of the right index finger and the right knee. There

were a few spots of possible folliculitis over the back of the left calf. The Birmingham Vasculitis Activity Score (BVAS) was elevated at 22, consistent with active vasculitis.

Investigations showed: haemoglobin 9.9g/dl, ESR 105 mm/h, creatinine 50 µmol/L, and creatine kinase 52 IU (normal). Urinalysis revealed ++ blood, ++ protein. Urine protein excretion was 0.52g/24h. A chest x-ray showed multiple cavitating lesions consistent with WG, MRI of the sinuses showed extensive sinus involvement but no evidence of bone destruction. A nasal biopsy from an area of granulation in the left nostril showed acute inflammation and ulceration. Anti-Neutrophil Cytoplasmic Antibodies (ANCA) were positive by indirect immunofluorescence with a cytoplasmic pattern and was strongly positive for proteinase-3 (PR3-ANCA) 255 IU (0-7). Myeloperoxidase ANCA (MPO-ANCA), anti-glomerular basement membrane antibodies and ANA were negative. A diagnosis of Wegener's granulomatosis was made.

She was admitted to the maternity unit and treated with oral prednisolone 1 mg/kg, and intravenous methylprednisolone 500mg daily for 3 days. The aim of treatment was to control the disease and maintain the pregnancy for as long as possible to permit a normal delivery. The initial plan was to consider induction of labour at around 34 weeks. She was reviewed regularly by her obstetrician, consultant rheumatologist and renal physician. Intravenous immunoglobulin 24 g/day for 5 days was added to steroid treatment. Chest x-ray was repeated after 5 days, and showed progression of the multiple cavitating lesions in both lungs. In view of this, further immunosuppression was felt to be required and, on day 5, azathioprine (target dose 2mg/kg/day) was started for remission induction and maintenance. She was prescribed prophylactic

Competing interests: none declared.

**Table I.** Cases of Wegener's granulomatosis *de novo* in pregnancy.

Author	Year	Design	No. of patients	Disease status	Treatment	GA at delivery or termination	Complication	Out come of pregnancy	Fetal outcome	Maternal outcome
Bessias <i>et al.</i> (5)	2005	Case report	1	De novo	P/Cyc	34 wk	Acute limb ischemia/PTD	c/s	good	Remission/ amputation of right limb
Sahni <i>et al.</i> (6)	2005	Case report	1	De novo	No treatment	–	–	–	good	Limited WG
Masterson <i>et al.</i> (7)	2004	Case report	1	De novo	Prednisolone and IVIG	34wk	PET, DM PTD	c/s	good	remission
Dayoan <i>et al.</i> (8)	1998	Case report	1	De novo	P/cyc	36 wk	SROM	VD	good	remission
Luisiri <i>et al.</i> (9)	1997	Case report	1	De novo	P/cyc	–	–	–	good	remission
Habib <i>et al.</i> (10)	1996	Case report	1	De novo	steroids / trimetho-primisulfa / cyc	18 wk	Acute abdomen Ischemic bowel	Medical termination	–	Resection of ischemic bowel
Field <i>et al.</i> (11)	1991	Case report	1	De novo	Steroids / cyc/ haemodialysis	33 wk	relapse	c/s	good	–
Palit& Clague (12)	1990	Case report	1	De novo	P/cyc	7 wk	–	Medical termination	–	remission
Milford & Bellini (13)	1986	Case report	1	De novo	Steroids / aza	25 wk	Intracranial bleeding	–	death	death
Talbot <i>et al.</i> (14)	1984	Case report	1	De novo	Steroids / cyc	28 wk	–	VD	–	–
Zlotnikova (15)	1975	Case report	1	De novo	–	–	–	–	–	–

P: prednisolone; Cyc: cyclophosphamide; Aza: azathioprine; IVIG: immunoglobulin; wk: weeks; VD: vaginal delivery; I.O.L: induction of labour; PET: preeclampsia; PPRM: premature preterm rupture of membrane; C/S: caesarean section; IVF: in vivo fertilisation; PTD: preterm delivery; DM: diabetes mellitus.

enoxaparin and her prednisolone was decreased to 50 mg/day. She was discharged after 9 days in a stable condition. She continued to make very good progress after discharge and her prednisolone was decreased gradually to 35mg daily whereas her azathioprine was increased to 150mg/day. Foetal growth as assessed by ultrasonography was normal. In view of the improvement in disease activity, it was decided to maintain pregnancy to 38 weeks gestation and then electively induce delivery. She delivered vaginally a healthy baby boy weighing 3000 g at 37 weeks 5 days, after elective induction.

Following delivery she was generally well with some grumbling disease within the nose and ears (BVAS = 6). A chest x-ray showed very good resolution of her previous pulmonary cavities. One day post partum, the maternal PR3-ANCA was 22 IU, and the infants PR3-ANCA was 58 IU. The prednisolone dose was reduced to 20 mg daily and azathioprine was maintained at 150 mg daily. Her subsequent progress has been complicated by persistent disease activity

within the ears and nose, lacrimal gland involvement, and pulmonary involvement. This has required intravenous cyclophosphamide therapy, mycophenolate mofetil and most recently B cell depletion with rituximab, to which she has responded well. Her most recent BVAS 2 years 3 months after presentation was 0.

### Discussion

Wegener's granulomatosis presenting during pregnancy is very uncommon, with only 11 previous cases documented and presents a major challenge (Table I). WG typically presents at age >40 years and therefore WG in pregnancy is an uncommon situation. Presentation of *de novo* WG occurs most frequently in the second and third trimesters. The foetal outcome is generally good, although there was one foetal death. The pregnancy of a woman developing WG at seven weeks of gestation was medically terminated. There was one maternal death due to intracranial bleeding, her foetus also died. In our case the neonate was shown to be PR3-ANCA positive suggesting

transplacental passage of ANCA. He has, however, never shown any signs of WG. There is a previous single case of MPO-ANCA placental transmission with induction of a pulmonary renal syndrome (1).

The treatment of *de novo* WG in pregnancy is difficult as the risk of treatment must be balanced against the risk to both the mother and her foetus. Close collaboration is needed between physician and obstetrician. Renal involvement may be difficult to differentiate from pre-eclampsia. Most immunosuppressive drugs are either contraindicated or should only be used with caution during pregnancy (2). Alkylating agents, including cyclophosphamide, have been shown to possess mutagenic, teratogenic and carcinogenic potential when used early in the pregnancy. However, cyclophosphamide is considered to be safe in the third trimester of pregnancy. Our patient was at 30 weeks of gestation and teratogenicity was not a major concern. Our patient presented with multisystem disease with potential life threatening

involvement (haemoptysis due to pulmonary vasculitis). Current guidelines for the management of multisystem active vasculitis are induction with corticosteroids and cyclophosphamide (3, 4). Extensive discussion was had with the patient, her partner and other experts. The consensus was to avoid the use of cyclophosphamide if possible. Our strategy therefore was to attempt to induce disease remission as speedily as possible with the aim of maintaining pregnancy for as long as possible. We therefore choose an induction regime of high dose corticosteroids, intravenous immunoglobulin and azathioprine. In the short term this achieved our immediate goal of controlling disease activity as evidenced by an improvement in clinical state with a fall in BVAS score. We were able to maintain pregnancy until 38 weeks. However, her subsequent course has been characterised by grumbling disease with a persistently elevated BVAS score requiring pulse intravenous cyclophosphamide and rituximab. It is possible that although the initial treatment was successful in the short term it did not induce a sufficiently robust

and durable remission, which we might have achieved had we used cyclophosphamide initially.

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