

Pregnancy in patients with Wegener's granulomatosis: report of five cases in three women

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Abstract

Five cases of pregnancy occurring in three women with previously diagnosed Wegener's granulomatosis are described. The disease was diffuse in one case and localised in the other. Initial treatment consisted of a combination of corticosteroids and intravenous cyclophosphamide in two women, and methotrexate in one. Four pregnancies ended in live births despite pre-eclampsia in two cases. One therapeutic abortion was induced because of encephalocele. Comparable reported cases were reviewed to examine the implications of immunosuppressive treatment on the fetus. A relapse occurred during pregnancy in 40% of the cases, but in 25% if only pregnancies beginning during inactive disease were taken into account. No other indicator for maternal and fetal outcome was obvious. Pregnancy should be planned after complete disappearance of disease activity. In the case of a relapse a combination of immunosuppressive drugs and corticosteroids should be chosen rather than corticosteroids alone because the outcome of pregnancy is poor in cases of undertreatment. Prematurity remains common.

(*Ann Rheum Dis* 2000;59:800-804)

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Accepted for publication
9 March 2000

Case reports

CASE 1

A 30 year old woman with type I diabetes mellitus since the age of 20 was pregnant in 1990 and 1992, with full term deliveries by caesarean section for dystocia. She presented in October 1993 with a three month history of otitis media, sinusitis, haemoptysis, and arthralgias. A chest radiograph displayed mild bilateral infiltrates. Alveolar haemorrhage was confirmed by bronchoalveolar lavage study. There was no renal disease. Histological examination of a nasal biopsy specimen showed giant cell granuloma and necrotising leucocytoclastic vasculitis. Cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were positive with antiproteinase 3 specificity. Monthly 1 g intravenous cyclophosphamide pulses together with prednisone 1 mg/kg daily were started. Remission was achieved within three months, with negative c-ANCA. Cyclophosphamide was stopped in February 1995 (cumulative dose 18 g) and prednisone was progressively tapered to 5 mg daily in August 1995. Maintenance treatment then comprised hydrocortisone 20 mg daily because of adrenal insufficiency, associated with co-trimoxazole (320 mg trimethoprim and 1600 mg daily sulfamethoxazole) until August 1995. Co-trimoxazole was then withdrawn because she wanted to become pregnant. In January 1996 a therapeutic abortion was carried out at 12 weeks' gestation because of a massive fetal encephalocele. Serum folate level (without any supply), acetylcholinesterase electrophoresis, and fetal karyotype were normal.

A fourth pregnancy began in March 1996 while she was receiving hydrocortisone 20 mg daily. Obstetric echography was normal. The pregnancy was uneventful until October 1996. At 37 weeks, hypertension (150/90 mm Hg) with proteinuria ++, raised uric acid (525 $\mu\text{mol/l}$) and thrombocytopenia ($88 \times 10^9/\text{l}$) appeared without haemostasis, and liver enzymes were abnormal. No flare up of WG was obvious. ANCA testing remained negative. Caesarean section delivered a healthy 4170 g girl. APGAR scores were 8 and 10 at one and five minutes. No relapse of WG was noted while receiving hydrocortisone 20 mg daily.

A fifth pregnancy began in June 1999. Her WG was in remission with negative ANCA and she was receiving no treatment. The course of the pregnancy was uneventful except for the occurrence of a retroplacental haematoma in December. Subsequent ultrasound examinations showed its resorption. Delivery was

Wegener's granulomatosis (WG) is an uncommon systemic vasculitis of unclear pathophysiology. It usually affects the upper respiratory tract, the lungs, and the kidneys. Before the introduction of effective treatment the one year mortality rate was 82%. Currently, a combination of corticosteroids and cyclophosphamide induces remission in most patients,¹ but relapses are common and may occur several years after remission.² The incidence of WG peaks in the fourth and fifth decades with a slight male predominance. Hence, reports of pregnancy in patients with WG are few. Improvement of the prognosis of WG may increase the number of pregnancies monitored. The influence of pregnancy on WG and vice versa, the management of these patients taking into account possible life threatening complications of WG, and the potential teratogenic effect of immunosuppressive drugs should be precisely determined. We report five pregnancies in three patients with previously diagnosed WG and review previous similar reports in French and English publications.

induced by caesarean section at 35 weeks because of macrosomia. A 4620 kg healthy boy was born with APGAR scores of 10 at one and five minutes. At the present time her WG remains in remission without treatment, with negative ANCA. All the children are well.

CASE 2

A 27 year old woman had had a previous normal pregnancy three years previously when she complained, in April 1993, of a one month history of nasal obstruction, otalgias, arthralgias, and haemoptysis. Chest radiographs showed multiple bilateral nodules, one of them excavated. A histological study of a lung surgical biopsy specimen showed necrotic giant cell granuloma. Cough and rhinitis rapidly improved during treatment with prednisone 0.5 mg/kg daily. One month later, a relapse occurred. Her serum creatinine level rose from 280 to 509 $\mu\text{mol/l}$ in one week. A histological study of a renal biopsy specimen showed diffuse crescentic glomerulonephritis with severe tubulointerstitial inflammation. c-ANCA were positive with antiproteinase 3 specificity. Three pulses of methylprednisolone 1 g daily were started, followed by prednisone 1 mg/kg daily and monthly 750 mg intravenous cyclophosphamide pulses. Remission was achieved within four months, with negative c-ANCA and a dramatic drop in the serum creatinine level to 120 $\mu\text{mol/l}$. Cyclophosphamide was stopped in October 1995 (cumulative dose 13.5 g), and prednisone was progressively tapered to 5 mg daily together with co-trimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg daily).

She became pregnant in March 1997. Her prednisone dose was systematically increased to 10 mg daily and co-trimoxazole was stopped. In November 1997 hypertension (145/90 mm Hg) appeared with oedema in the legs, proteinuria (0.7 g daily), raised uric acid (327 $\mu\text{mol/l}$), but a stable serum creatinine level, normal platelet count, and normal liver enzymes. No flare up of WG occurred. ANCA testing remained negative. At 35 weeks after an induced vaginal delivery she gave birth to a 3120 g healthy boy. The APGAR score was 10 at one and five minutes. After three years' follow up, mother and child are well. No relapse of WG was seen while receiving co-trimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg/daily) and prednisone 5 mg daily.

CASE 3

A 20 year old woman complained in 1984 of chronic rhinitis and otitis media complicated with mild hearing loss. Two years later, acute dyspnoea and dyspnoea led to the discovery of subglottic stenosis. A histological examination of a tracheal biopsy specimen showed necrotic giant cell granuloma. ANCA testing was negative. Treatment comprised laser vaporisation that was initially successful, but several relapses occurred needing successive laser treatments. In 1990 a solitary excavated nodule was discovered by thoracic x ray examination. Rhinitis and laryngitis were present without

sinusitis or renal disease. Subglottic stenosis was stable. ANCA testing was negative. Co-trimoxazole (trimethoprim 160 mg and sulfamethoxazole 800 mg twice daily) was started with success, but a relapse occurred four years later as the patient withdrew herself from this treatment. Bronchoscopic dilatation was associated with prednisone 1 mg/kg daily and methotrexate 7.5 mg weekly. In 1997 she wanted to become pregnant again and methotrexate was stopped. When pregnancy was diagnosed, prednisone 20 mg daily was started. The course of her pregnancy was uneventful apart from diabetes, which was treated. At 39 weeks a caesarean section was carried out because of dystocia; she delivered a healthy 3750 g boy. The APGAR score was 10 at one and five minutes. After one year's follow up, mother and child are well. No relapse of WG was seen despite a progressively decreased dose of prednisone.

Discussion

We report five cases of pregnancy in three women with biopsy proved WG. A longlasting remission before planning pregnancy was advised in all cases to avoid the teratogenic effect of drugs and relapse of WG. Four pregnancies ended in delivery of healthy eutrophic babies. No relapse of WG occurred.

Reports of pregnancy in WG are rare: 21 pregnancies in 17 patients with WG have been described in French and English language publications since 1970.³⁻¹⁸ WG was diagnosed during pregnancy in six cases that ended in three premature births,^{3 11 17} two therapeutic abortions^{5 13} and one maternal death.⁴ Six cases of WG onset or relapse occurred in the two to eight weeks' postpartum period.^{7 10 12 13 18 19} Apart from the present report, 15 pregnancies were reported in 11 patients with known WG (the case of Fields *et al*⁶ should also be included, though WG was diagnosed after pregnancy, because pauci-immune glomerulonephritis was treated with cyclophosphamide and corticosteroids) (tables 1 and 2). Mean age at pregnancy was 24.6 years (range 20-30). Five patients had become pregnant before disease onset. All patients had been treated with corticosteroids, together with azathioprine in five patients, and cyclophosphamide in eight. Cyclophosphamide was given orally in four cases with various lengths of treatment: 6,^{6 8} 12,⁹ or 18 months.¹⁶ It was given intravenously in four cases with varied cumulative doses: 1 g,^{7 15} 3 g,⁷ and 23 g.¹⁸ Of note, two of our patients became pregnant after at least 16 cyclophosphamide pulses.

Oral contraception is usually prescribed during cyclophosphamide treatment because of its teratogenic effect and to preserve ovarian function.^{8 16} Fecundity after intravenous cyclophosphamide treatment has been well studied in systemic lupus. The incidence of ovarian failure varied between 11% and 59%.²⁰ The main risk factors for ovarian failure were higher age at cyclophosphamide onset and cumulative dose.²⁰ No similar data about cyclophosphamide induced sterility are available for systemic

Table 1 Pregnancies in patients with a known Wegener's granulomatosis (WG) or WG before pregnancy active at pregnancy onset

Author, reference	Age at WG onset (years)	Organs initially affected*	Initial treatment†	Age at pregnancy (years)	Organs affected at pregnancy onset	Complication/ treatment	Pregnancy outcome
M'Rad ¹²	24	E, L, S, A	CS	25	E, S, L, K	Relapse (L, S) oCY	Therapeutic abortion Maternal death
Pauzner ⁸	30	E, L, K, S	oCY, CS AZA TS	P2‡:32		Subglottic stenosis CS	Therapeutic abortion
Lima ⁷	24	E, L, S, A	pCY CS	24	S, A	Relapse T1‡ (L, S, A) CS	Spontaneous abortion
Kumar ¹⁶	22	E, K	oCY, CS	25	E, A	Relapse T1 (E, A) CS Postpartum flare (L)	Spontaneous abortion

*A = arthralgia or arthritis; E = upper respiratory tract (ear, nose, throat) and eyes; K = kidney; L = lung and lower respiratory tract; S = skin.

†AZA = azathioprine; CS = corticosteroids; CY = cyclophosphamide; oCY = oral CY; pCY = intravenous pulses of CY; TS = trimethoprim-sulfamethoxazole.

‡P2 = second pregnancy; T1 = first trimester.

vasculitides, probably because these diseases generally affect older patients.

The influence of pregnancy on the course of WG is not precisely known. No flare up of WG occurred during or after pregnancy in our patients. In the literature, eight of 15 pregnancies with known WG were complicated by a relapse. Four relapses occurred while pregnancy had begun during active disease^{7 8 12 16} and four while WG was in remission.^{6 8 14 15} WG activity at pregnancy onset seemed to be the main indicator of poor maternal and fetal prognosis as four of 15 pregnancies beginning during active WG ended in two spontaneous fetal deaths, one therapeutic abortion, and one maternal death despite therapeutic abortion.^{7 8 12 16} Clinical activity correlated with positive ANCA at pregnancy onset in two cases.^{7 16}

Four relapses occurred despite remitted WG at pregnancy onset.^{6 8 14 15} In two cases, ANCA remained positive despite clinical remission.^{8 15} ANCA monitoring was useful for individual

cases: persistently reduced ANCA titres associated with clinical remission suggest inactive disease and help to authorise pregnancy. Nevertheless, apart from in the context of pregnancy, ANCA titres do not have an absolute predictive value for WG activity. Relapse rate was 25% among 16 pregnancies occurring in inactive WG. Of note, the postpartum period was uneventful in all our patients.

The length of time elapsing between the end of WG treatment and pregnancy onset, even if longer than two years, was not sufficient to avoid the risk of relapse.^{14 16} However, pregnancy can be planned after a sufficiently longlasting remission. Of 15 pregnancies beginning in inactive WG, 14 ended in live births (one unrelated WG therapeutic abortion) (our patients and those reported in the following references).^{6-10 14 15 18}

A long prior course of immunosuppressive treatment before pregnancy, and maintenance treatment at the onset of pregnancy, do not

Table 2 Pregnancies in patients with a known Wegener's granulomatosis (WG) or WG before pregnancy in remission at pregnancy onset

Author, reference	Age at WG onset (years)	Organs initially affected*	Initial treatment†	Age at pregnancy (years)	Complication/ treatment	Pregnancy outcome‡ (weeks) / weight (kg)	Gestational age
Cooper ¹⁰	25	E, L	AZA, CS, Radiotherapy	ND	Respiratory infection treated with penicilline+ hydrocortisone	Membranes rupture induced VD 35/2.63	
Harrison ¹⁴	16	E, L	AZA, CS	P1‡: ND P2: ND P3: ND	Relapse (L) T3‡: Pre-eclampsia	Normal Normal Normal Caesarean section Twin	
Biesenbach ⁹	20	E, L, K	oCY, CS Renal transplant CS, CsA	22		33/1.350-1.18 Caesarean section 33/2.04	
Fields ⁶	18	E, L, K, S, A	CY, CS	23	T2: Relapse (E, L, S, K) oCY + CS + haemodialysis	VD 38/2.77	
Pauzner ⁸	30	E, L, K, S	OCY, CS AZA TS	P1: 31	T2: Relapse OS + laser	VD 40/3.17 VD 39/3.74	
Lima ⁷	29	E, A	pCY AZA, CS	P1: 32 P2: 33	T2: Relapse (E, L, K) oCY + CS AZA + CS	Induced VD 37/2.87	
Parnham ¹⁵	21	L, K, S, A	PC, PE, CS, CS TS	24	Oligohydramnios Postpartum relapse	Normal ND/3.56	
Koldingsnes ¹⁸	23	E, K	CS pCY AZA, CS	28		Therapeutic abortion for encephalocele Caesarean section 37/4.17 Caesarean section	
Present report No 1	30	E, L, A	pCY, CS Hydrocortisone, TS	P1: 32 P2: 33 P3: 35	Pre-eclampsia Retroplacental haematoma Macrosomia Pre-eclampsia	35/4.62 Induced VD 35/3.12	
Present report No 2	27	E, L, K, A	pCY, CS pCY, CS, TS	31		Caesarean section 39/3.75	
Present report No 3	20	E, L	Laser TS MTX, CS	34	Dystocia		

*A = arthralgia or arthritis; E = upper respiratory tract (ear, nose, throat) and eyes; K = kidney; L = lung and lower respiratory tract; S = skin.

†AZA = azathioprine; CS = corticosteroids; CsA = cyclosporin; CY = cyclophosphamide; oCY = oral CY; pCY = intravenous pulses of CY; MTX = methotrexate; PE = plasma exchanges; TS = trimethoprim-sulfamethoxazole.

‡P1, P2, P3 = first, second, third pregnancy; T1, T2, T3 = first, second, third trimester.

¶VD = vaginal delivery; ND = no data.

seem able to prevent relapse.^{6 8 16} Among seven well documented relapses during pregnancy, WG treatment at pregnancy onset comprised prednisone,¹² cyclophosphamide plus prednisone,⁷ co-trimoxazole in two cases,^{8 15} while three patients had no treatment.^{6 8 16} Among seven well documented pregnancies with no relapse (Harrison's letter provided no information about maintenance treatment¹⁴), WG treatment at pregnancy onset varied between no treatment in three cases (case No 3 and the report by Lima⁷, hydrocortisone (case No 1), co-trimoxazole and prednisone (case No 2), azathioprine and prednisone,¹⁰ cyclosporin and prednisone in one twin pregnancy.⁹

The risk of relapse during pregnancy also does not correlate with the initial severity of WG. Occurrence of a relapse seems to be a priori unpredictable. This suggests the true influence of pregnancy on the course of WG.⁸

Implications of WG treatment according to pregnancy state and disease severity have been discussed by several authors.^{11 16 17}

Cyclophosphamide is contraindicated during pregnancy, but data on its real fetal toxicity are limited.^{3 6 11 15 17} Induced delivery was also indicated in order to shorten contact of the fetus with cyclophosphamide.¹¹ Patients treated with a combination of immunosuppressors and corticosteroids had a more favourable pregnancy outcome^{6 9 15} than those treated with corticosteroids alone.^{7 8 12 16}

Considerable experience has proved that azathioprine is safe during pregnancy. However, it is less effective than cyclophosphamide in WG.

Methotrexate is strongly contraindicated during pregnancy because of its early teratogenicity, referred to as the "aminopterin syndrome",²¹ and late fetal bone marrow toxicity.¹¹ The critical period for teratogenicity is suspected to be between six and eight weeks after conception. Fetal exposure from 10 to 32 weeks after conception has not resulted in obvious malformations.²²

Because of its folic acid antagonism, the manufacturers of co-trimoxazole advised against its use during pregnancy. Hence, this drug has been stopped in two of our cases. In the case of pregnancy with encephalocele, co-trimoxazole cannot be incriminated as it was stopped several months before conception. A large case-control study concluded that co-trimoxazole does not have a teratogenic effect.²³ As a clear preventive effect of co-trimoxazole on WG relapse has been shown,²⁴ its continuation during pregnancy should be discussed.

High dose immunoglobulins have been proposed in second line treatment in WG.²⁵ They have never been evaluated in WG pregnancy,¹⁶ but in other conditions, such as antiphospholipid syndrome,²⁶ they appeared to be safe.

Two patients developed pre-eclampsia in the third trimester. Diabetes, renal WG sequelae, or corticosteroids were present as risk factors. In the literature, pre-eclampsia was seen in one of eight patients with previous WG renal disease⁹ and in another patient with WG

diagnosed during pregnancy.¹¹ All four patients with pre-eclampsia were treated with corticosteroids. Pre-eclampsia should be distinguished from a flare up of WG by clinical and laboratory criteria, such as absence of hypertension (which is rare in a WG flare), presence of extra-renal manifestations, especially upper airways and lung disease, and ANCA titres.

Prematurity is common in WG pregnancies. Mean duration of gestation was 36 weeks (range 33–40).^{6–10 15} Corticosteroids use also seemed to be a risk factor for preterm delivery and pre-eclampsia in pregnant women with antiphospholipid syndrome.²⁷

In conclusion, in patients with known WG, pregnancy may be authorised if the disease remains clinically inactive with longlasting remission while no treatment or co-trimoxazole treatment is given. Long term cyclophosphamide treatment does not systematically imply sterility. A flare up of WG may occur during pregnancy in more than one quarter of cases, but no predictive factor seems to be significant. Pre-eclampsia and prematurity associated with corticosteroids or prior renal disease are the most serious complications. Hence, these pregnancies should be considered as high risk and need careful monitoring by both obstetrician and doctor, similar to the monitoring required in other systemic diseases such as systemic lupus erythematosus.

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