Successful completion of pregnancy in a woman with chronic granulomatous disease

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Summary: Chronic granulomatous disease (CGD) used to be a fatal illness of childhood and patients rarely survived past the first decade. Although antimicrobial prophylaxis has dramatically reduced mortality and morbidity in recent years, CGD remains a life-threatening condition. We present the successful obstetric course of a patient with CGD.

Keywords: chronic granulomatous disease, pregnancy, antimicrobial prophylaxis, neutrophil oxidative burst activity

INTRODUCTION

Chronic granulomatous disease (CGD) is an inherited immunodeficiency disorder caused by defects in NADPH oxidase subunits (gp91phox, p47phox, p22phox, p67phox and p40phox) expressed in phagocytes (neutrophils, monocytes and macrophages). These enzymatic defects result in an inability to kill catalase-positive bacteria and fungi and render the patient susceptible to recurrent life-threatening infections, such as sepsis, pneumonia and meningitis. Patients with an X-linked form of CGD caused by a defect in the gene encoding gp91phox appear to have a more serious clinical phenotype than those with autosomal-recessive forms caused by defects in the other four genes. Antimicrobial prophylaxis and aggressive management of these infections have dramatically reduced infectious complications, but CGD remains a life-threatening condition.

A patient with CGD was referred to us from a senior paediatrician because of her desire to become pregnant. However, little is known of the clinical course, management and risk of infection in such cases. We present the successful obstetric course of a patient with CGD and document the management, immunological laboratory changes, and neutrophil oxidative burst activity during pregnancy.

CASE REPORT

The patient had a mutation in the *CYBA* gene encoding p22phox, a small subunit of membrane-bound flavocytochrome b558. She had been hospitalized several times for recurrent bacterial infections, such as pneumonia, lymphadenitis, subcutaneous abscess and blepharitis. She had been in relatively good health taking cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis

into adulthood, except for a severe infection in her first pregnancy at 29 years of age. Then, following a uterine infection with *Burkholderia cepacia* complex, clinical findings of haemophagocytic syndrome (HPS) and septic pulmonary embolism developed. She underwent aggressive treatment with multiple antibiotic combinations and immunosuppressant agents (prednisolone and cyclosporin A). Although her pregnancy ended in a spontaneous miscarriage at seven weeks of gestation, she recovered completely from the serious infectious complications of HPS two months later.¹

The patient became pregnant again at 31 years of age. Based on her previous miscarriage caused by infectious complications, it was clear that the pregnancy was potentially high risk and it was essential to devise a management strategy for the CGD. Cotrimoxazole prophylaxis was continued at the same dosages used before pregnancy (160 mg of trimethoprim and 800 mg of sulfamethoxazole per day). Folate was replenished in the first trimester. At every obstetric visit, inflammatory markers such as the white blood cell count, serum C-reactive protein and blood 1,3-beta-D glucan were measured to ensure an early recognition of any occult bacterial and fungal infections. To evaluate whether pregnancy affected neutrophil function, we performed dihydrorhodamine 123 (DHR)-staining flow cytometry analysis of the patient's neutrophil oxidative burst activity. Whole leukocytes were incubated with DHR after being treated with catalase. The leukocytes were then stimulated with phorbol 12-myristate 13-acetate and analysed by flow cytometry, with gating based on forward- and side-scatter properties.

The course of pregnancy was uneventful. No significant increases in the levels of blood inflammatory markers or 1,3-beta-D glucan were observed during pregnancy (Table 1). To investigate the immunological changes during pregnancy, we performed immunologic tests, such as evaluating lymphocyte subsets, natural killer (NK) cell activity and lymphocyte blastoid transformation by phytohemagglutinin (PHA) in each trimester of pregnancy. The proportions of lymphocyte

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Table 1 Blood tests in each trimester of pregnancy

Blood tests	Normal range	Trimester		
		First	Second	Third
CD4 (%)	25.0–54.0	29.4	25.7	27.7
CD8 (%)	23.0–56.0	39.3	48.0	46.5
CD4/CD8 (ratio)	0.4–2.3	0.80	0.54	0.60
CD3 (%)	58.0–84.0	74.8	79.3	70.7
HLA-DR ⁺ CD4 ⁺ (%) [*]	1.0–12.0	5.1	2.9	2.8
HLA-DR ⁺ CD8 ⁺ (%) [†]	2.0–27.0	6.9	4.3	7.6
HLA-DR ⁺ CD20 ⁺ (%) [‡]	–	7.0	6.4	7.6
CD3 ⁺ CD161 ⁺ (%) [§]	–	24.3	33.8	39.3
Th1/Th2 (ratio)	3.8–25.0	25.0	16.1	18.2
NK cell activities (%)	18–40	36	16	14
Lymphocyte blastoid transformation induced by PHA (cpm)	20,500–56,800 (background: 127–456)	33,000	37,900	49,800
WBC (/μL)	3500–9100	8620	8770	6640
CRP (mg/dL)	≤0.3	0.3	0.7	0.4
β-D glucan (pg/mL)	≤20.0	5.1	5.8	5.4

PHA, phytohemagglutinin; NK, natural killer; WBC, white blood cell; CRP, C-reactive protein

^{*}Activated CD4-positive T-cells

[†]Activated CD8-positive T-cells

[‡]Activated CD20-positive B-cells

[§]NKT-cells

subsets, the lymphocyte response to PHA, and NK cell activity levels were all within normal ranges (Table 1). The neutrophil oxidative burst activity improved markedly as gestation progressed (Figure 1). The patient reached 40 weeks of gestation, but with an unfavourable cervix for inducing labour. Although vaginal delivery is considered the ideal mode of childbirth, we opted for an elective caesarean delivery at 40 weeks of gestation to avoid the risk of infection from prolonged labour. She delivered a 2930 g female baby with APGAR scores of 8 and 9 at one and five minutes, respectively; no congenital defects or severe hyperbilirubinaemia were observed. Cefazolin was given prophylactically to the mother for three days after delivery. No clinical evidence of postpartum infection was found.

DISCUSSION

In recent years, the routine use of antimicrobial prophylaxis has reduced the mortality and morbidity in patients with CGD.^{2–4}

A registry-based study in the UK and Ireland showed that the estimated survival was 88% at age 10 years and 55% at 30 years.⁵ Thus, such patients often survive into adulthood. Although it is likely that more women with CGD will wish to become pregnant in the future, only a few such cases have been reported to date. Our patient had a strong desire to become pregnant, but her first pregnancy triggered life-threatening infections (severe bacteraemia and bacterial-associated HPS) and eventually resulted in a spontaneous miscarriage. Blanco *et al.*⁶ reported that the incidence of bacteraemia was 7.5 per 1000 obstetric admissions and that no deaths or episodes of septic shock were found among obstetric patients with documented bacteraemia. However, CGD is still a life-threatening condition and pregnancy increases the opportunity of bacterial infections and is a high-risk time for women with this condition. Additionally, these infectious complications are likely to cause high-risk pregnancies.

We considered that the essentials of managing CGD during pregnancy are the early diagnosis of infections, antimicrobial

Figure 1 Dihydrorhodamine 123-stained flow cytometry of neutrophil oxidative burst activity after stimulation with or without phorbol 12-myristate 13-acetate

prophylaxis and aggressive treatment of infectious complications. Although no randomized trials have been reported on the effect of antibacterial prophylaxis in patients with CGD, several retrospective studies have suggested that cotrimoxazole therapy decreases the incidence of bacterial infections.^{2,7-9} Our patient received antibacterial prophylaxis with cotrimoxazole during pregnancy, and it was necessary to inform her about the clinical usefulness and safety of this treatment. The clinical usefulness of cotrimoxazole prophylaxis for pregnant women with CGD is unknown. Walter *et al.*¹⁰ observed that cotrimoxazole prophylaxis when begun at >14 weeks of gestation decreased the incidences of neonatal mortality, clinical chorioamnionitis and preterm delivery among human immunodeficiency virus (HIV)-infected pregnant women with low CD4 cell counts. In HIV/AIDS treatment guidelines,¹¹ cotrimoxazole for pregnant women with low CD4 cell counts is only recommended after the first trimester of pregnancy to avoid the potential teratogenic effects of trimethoprim. Trimethoprim is a folate antagonist (dihydrofolate reductase inhibitor), and its use during the first trimester might result in structural defects in the fetus, including cardiovascular defects and neural tube defects. Nevertheless, maternal supplementation with folate can reduce the risk of these congenital defects; in this case, we maintained the patient's normal concentration of folate in plasma during the first trimester using appropriate supplementation. Sulfamethoxazole does not appear to pose significant teratogenic risks, although it is capable of causing toxicities such as jaundice and hemolytic anaemia in the newborn. Therefore, despite a history of severe infection, we were able to prevent serious infections during this patient's pregnancy and in the perinatal period with no side-effects from medication or other problems in the newborn. Interestingly, flow cytometry of DHR-labelled neutrophils showed that the neutrophil oxidative burst activity was markedly improved with gestation. Similar phenomena during the pre- and perinatal periods have been described in a carrier of X-linked CGD and in normal healthy subjects.^{12,13} This successful clinical course in a pregnant woman with CGD has provided valuable data and we hope that this report will be helpful in the treatment of such patients who might wish to become pregnant.

DECLARATIONS

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