

Successful twin pregnancy in a patient with ulcerative colitis using azathioprine during conception

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ABSTRACT

Inflammatory bowel disease (IBD) frequently affects young patients of childbearing age. Treatments for inflammatory bowel disease include immunosuppressive, cytotoxic and surgical therapies. Azathioprine is frequently used to treat patients with steroid dependent IBD. We report the case of a patient with ulcerative colitis, treated with azathioprine prior to conception and during the subsequent pregnancy with the subsequent successful delivery of healthy twins. Although some potential risks indeed exist, the use of AZA may not be harmful to the mother or the fetus in many instances.

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Inflammatory bowel diseases affect young patients during their reproductive years (1). The control of disease activity before conception and during pregnancy is of paramount importance to optimize both maternal and fetal health. Generally, if the disease is inactive at the time of conception and during pregnancy, the fetal outcome of an IBD patient is similar to that observed in the general population (1). A meta-analysis by Miller et al (2), including more than 1,300 females with ulcerative colitis (UC) and over

700 patients with Crohn's disease (CD), reported a normal pregnancy in 85% of women with UC (76-87% in individual studies) and in 83% of women with CD (71-93% in individual studies). Fetal malformations were observed in about 1% of all pregnancies and the frequency of spontaneous abortions and stillbirths was similar to that observed in the general population (2).

A 32 year old woman was in follow-up at our department from 1992 for UC (colonoscopically documented pancolitis). The patient was treated with mesalazine and disease activity was quiescent until August 2006, when the patient was admitted with bloody diarrhea (up to 20 episodes/day), weakness, fever (up to 38.5°C), and appearance of pustular ulcerated cutaneous lesions in both

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forearms and shoulders. Routine blood tests were performed, including inflammatory markers. Results showed anaemia (Hb 10.2 g/dl) and raised C reactive protein. An abdominal x ray showed toxic megacolon, with marked dilation (> 6 cm) of left colonic flexure, arterial blood gases showed evidence of a metabolic alkalosis. A clinical diagnosis of an acute flare up of UC was made. The patient was treated with intravenous steroids and antibiotics (prednisone, 80 mg/day, ciprofloxacin, 400 mg/day, plus metronidazole, 1.5 g /day). General conditions improved after some days of therapy; a skin biopsy showed a picture suggestive of gangrenous pyoderma. Azathioprine (AZA) therapy (2 mg/Kg /day) was started. The patient was advised to avoid pregnancy. Three months after starting AZA the patient was pregnant. Aza therapy was continued throughout pregnancy. At the end of the pregnancy twins were born. Breast feeding was forbidden. 3 years after delivery, the mother (still continuing AZA therapy) shows complete remission of colonic and skin disease; the two children enjoy good health and show normal growth.

Approximately 25% of female patients conceive after a diagnosis of IBD (3). These patients are more likely to experience pre-term labour (< 37 weeks duration) and deliver low-birthweight babies (> 2500 g) (3). It is generally thought that adverse effects in IBD pregnancy are related to the disease activity rather than to the drugs given to treat these conditions (4).

The "right time" to conceive is usually suggested during complete disease remission, since active disease is a risk factor for pre-term delivery and low birth weight (3). Most of the experience and literature data concerning AZA and 6-mercaptopurine (6-MP) therapy during pregnancy originates from renal transplant patients (5), in whom no significant increase in congenital anomalies have been described.

Alstead and colleagues (6) studied retrospectively 16 pregnancies in 14 women receiving AZA for IBD

and identified only one infectious complication (hepatitis B virus infection) during pregnancy, without evidence of congenital abnormalities or subsequent health problems in these children. Francella and colleagues (7) compared 40 women using 6-MP before the time of conception with 37 using the drug at the time of conception or during the entire pregnancy, and did not find statistical differences between the two groups with respect to spontaneous abortion, abortion secondary to birth defects, major congenital malformation, neoplasm or increased infections. O'Connell and colleagues (8), on the other hand, remarked that in Francella's study only 15 patients used 6-MP during the entire pregnancy, with a dosage variable from 25 to 175 mg/day. In this group, 10 patients had full term pregnancy, with two children having major infections, another presented major congenital abnormality and a further child displayed minor congenital abnormality. Goldstein et al (9) studied 189 women taking AZA during pregnancy (mean dosage 50-100 mg/day) compared with a control group of 230 women; no difference concerning major malformations were found, although in AZA group an increased percentage of lower birth weight and premature delivery was noted. In a Danish study (10) of 76 pregnancies in 69 women using AZA or 6-MP, a higher risk of adverse birth outcome (pre term birth 26.2% vs 4.6% of control population, low birth weight at term 4.2% vs 1.4%, congenital abnormalities 9.4% vs 3.9%) was found, but the authors suggested that this adverse outcome may be more due to IBD activity rather than drug therapy. In another study investigating 9 pregnancies (5 with CD, 1 with UC) using AZA or 6-MP 30 days before conception or during the first trimester (11), one case of aphakia and one case of multiple malformations were reported. This study was compared with 19,418 controls and the risk in markedly increased (22.2% in AZA-6-MP group against 3.7% in control group). In another study (12) investigating pregnancies fathered by men in therapy with AZA or 6-MP, the investigators

concluded that, since there were no differences between conceptions obtained by fathers using or not using these drugs, such immunosuppressive therapy should not be discontinued.

The use of AZA and 6-MP in pregnancy appears safe and well tolerated (13), as also shown from our experience, and recent guidelines for IBD management in adults (4,14) suggest that AZA should be continued during pregnancy because the risks to the fetus due to disease activity appears greater than risks due to drug toxicity. In addition, a recent study on a large group of subjects treated with these drugs did not show increased number of infections in their breastfed children (15).

Although there may be a slight increased risk of congenital malformations, growth restriction and preterm delivery in infants exposed to AZA in early pregnancy (16), these associations may be confounded by the severity of maternal illness, and the use of this drug seems overall safe (17), as also confirmed by a recent trial on a large cohort (18). Women with IBD are concerned about the risks of drug therapy, especially when pregnant. Patients with IBD need to be aware risks of drug therapies and active IBD during pregnancy for the foetus (19).

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