

# Resolution Of Male Infertility Following Anti-Tumor Necrosis Factor (Infliximab): A Case Report

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## Abstract

Male infertility, present in 5% of the Western population, is more prevalent in patients with Crohn's disease (CD). CD is active during the reproductive years; therefore the treatment being used might have an impact on the fertility of the patient. Experience with anti-tumor necrosis factor (anti-TNF) modulators has primarily been limited to women with rheumatoid arthritis and, thus the effect on male infertility has not been evaluated. Among females with CD clinical trials with anti-TNF necessitated abstinence from pregnancy. We report a case of resolution of infertility in a 28-year-old childless man with moderate to severe CD, who had infertility secondary to astheno-terato-spermia. Three attempts at artificial intrauterine insemination with the patient's sperm were unsuccessful. The patient received 5 mg/kg IV anti-TNF (Infliximab) for CD and 10 days later reported, for the first time in 8 years, enhanced libido and sexual activity. About 6 weeks later his wife became pregnant and subsequently delivered, at term, a small-for-age 2,100-g female infant. The child is now 9 months old and has there has been no report of any developmental disabilities. Subsequent sperm counts of the patients were deemed unnecessary. This is the first case report of a rapid resolution of male infertility following anti-TNF treatment and birth of a healthy infant in a previously infertile man with CD.

## INTRODUCTION

Conventional medicines to treat inflammatory bowel disease (IBD) include salicylates, corticosteroids, 5-ASAs, immunosuppressives, and infliximab. Adverse side effects from such medications include bone marrow suppression, diarrhea, hepatitis, pancreatitis, and infertility. Male infertility, occurring in about 5% of the Western population, is more prevalent among patients with Crohn's disease (CD). Drug impacts on fertility are especially pertinent to CD patients, as CD is primarily active during the reproductive years. There is no report in the literature of an IBD patient regaining fertility one month after commencing treatment with immunosuppressive agents. On the contrary, patients with IBD can have infertility due to the deleterious effect of sulfasalazine on sperm morphology. We present a case of resolution of male infertility in CD treated with Infliximab.

## CASE REPORT

A 28-year-old male with CD, previously treated with sulfasalazine and 5-ASA since the age of 20, was unsuccessful at impregnating his wife for more than one year. The patient's wife, a healthy 27 year-old non-smoker, with no prior medical history, was not on medications and neither had problems with infertility nor a history of procedures that could cause infertility. Subsequent

examination of the patient showed a low sperm count with abnormally structured sperm. Beginning April 2001, sulfasalazine and 5-ASA treatments were terminated and Infliximab was initiated. At the end of that month, the wife conceived and subsequently, a healthy female was born at term, but was small for gestational age (2.1 Kg).

By three months of age, however, the child's weight was 3,550g, which is appropriate for that age, and showed developmental milestones appropriate for three months.

## DISCUSSION

IBD is accompanied by a variety of extra-intestinal manifestations, including nutritional and metabolic complications, anemia of chronic disease, and electrolyte disturbances. Musculoskeletal complications, such as arthritis, peripheral arthralgias, and ankylosing spondylitis, and complications involving the skin and mucous membrane, such as erythema nodosum, pyoderma gangrenosum, aphthous stomatitis can also occur.

Initial medical treatment of IBD, include sulfasalazine, 5-ASA, prednisone, and immunomodulators, such as azathioprine and methotrexate. Known side effects of these medications include bone marrow suppression, diarrhea, hepatitis, pancreatitis, and infertility.

Di Paolo et al., in their study of the long term effects of sulfasalazine and 5-ASA on patients with UC, noted infertility in all patients on sulfasalazine, which improved when substituted with 5-ASA (2). Moody et al., evaluating whether IBD patients treated with sulfasalazine had similar rates of fertility and congenital malformation as compared to the general population, concluded that not only does sulfasalazine induce morphological abnormalities in spermatozoa but also may increase the risk of congenitally abnormal offspring (3). Burnell et al. compared the fertility of 70 men with CD with a group of age-matched controls and noted an association of CD with a significant reduction in family size, independent of steroid or sulfasalazine treatment (4).

In two recent studies, Infliximab, a chimeric monoclonal antibody against tumor necrosis factor, was shown to be effective at inducing remission of CD (5, 6). In the first study, approximately two thirds of the patients with moderately active CD and who received a single infusion of infliximab had a significant reduction in their score on a standard Crohn's Disease Activity Index. And, of these, approximately half (one third of the total) achieved actual clinical remission of CD. Although, the response was quite prompt, usually within 2 weeks, the durability of the response ranged from a few weeks to six months or greater (5). This pattern of response was mirrored in the second study, in which patients with perianal and cutaneous fistulas received three infusions over a period of six weeks (6). Since Infliximab was approved for use in the United States, the experience in treating patients in routine practice (7,8,9) has largely resembled that observed in the 2 controlled studies (5, 6).

As yet, the effects of Infliximab on human infertility are unknown. No impairment in reproductive success was observed in a fertility and general reproduction toxicity study conducted with mice and using an analogous antibody that selectively inhibits the functional activity of mouse TNF alpha (10). The teratogenic potential of Infliximab is also unknown. Whether it can cause fetal harm when administered to a pregnant woman or can adversely affect fertility needs further investigation (10). As of October 2001, there were 102 pregnancies identified with exposure to

Infliximab. Among the 54 pregnancies with known outcomes, 36 resulted in live births, 10 in miscarriage, and 8 in therapeutic termination. Of the live births, 2 infants were delivered with complications from CD mothers and one preterm infant died 3 weeks following birth. One medically confirmed case of congenital anomaly of tetralogy of Fallot has been reported (11). Infliximab should be given to pregnant women with caution. Furthermore, data are lacking on the effects of Infliximab on the offspring of male patients treated with Infliximab.

Infliximab may aid male infertility in IBD patients. However, additional research is needed to examine the effects of Infliximab on sperm count, structure, and motility.

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