

## INFLIXIMAB USE DURING PREGNANCY REVISITED

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To the editor,

A 39-year-old lady was seen for her complaints of low back pain, swelling in her right shoulder and right knee joints. She also described morning stiffness of two hours. She had been followed with the diagnosis of seronegative spondyloarthropathy for the last 16 years with concomitant four episodes of uveitis in the last 10 years. Her previous medications comprised different combinations of several non-steroidal antiinflammatory drugs (NSAIDs), sulphasalazine, colchicine, methotrexate, prednisolone and chloroquine. She declared that she could have not benefitted completely from any of these regimens. Her medical history was otherwise noncontributory.

The physical examination revealed limited motions in the cervical and low back regions; arthritic findings in the right shoulder and knee joints. Lumbar Schober was 3 cm. Chest expansion was 4 cm. Fabere test was positive bilaterally. Laboratory results were as follows: hemoglobin 10.7 g/dL, erythrocyte sedimentation rate (ESR) 50 mm/h, C-reactive protein (CRP) 3+, rheumatoid factor negative. Radiological evaluations showed bilateral grade 2 sacroiliitis. She was accordingly diagnosed to have ankylosing spondylitis. Keeping in mind the ineffectiveness of the aforementioned treatment alternatives, she was started on 3 mg/kg infliximab every eight weeks after the initial loading protocol (in accordance with the anti-TNF treatment guideline) along with daily indomethacin.

On the control visit after one month of infliximab therapy, 80% reduction was achieved both with regard to joint pain and limitations. Morning stiffness decreased to 15 minutes. ESR was 32 mm/h and CRP was negative. Thereafter, she continued the protocol every eight weeks with similar clinical outcome.

On the 18th month of treatment, she decided to plan for pregnancy. The patient was informed about the possible adverse effects of infliximab on

pregnancy and she was strictly instructed to stop the ongoing treatment protocol. The expected high risk of disease relapse on drug discontinuation was also explained to her. Accordingly, she has stopped the treatment and became pregnant three months after the last infusion. After an uneventful 10 weeks of gestation, she suffered from uveitis, generalized arthritis with stiffness lasting the whole day. Her daily activities were significantly impaired. After consulting the obstetrician, she was followed with paracetamol and NSAIDs for three weeks. As these drugs failed to improve her increasing complaints, she was commenced on a 3 mg/kg infliximab infusion after consulting once again the obstetrician and after getting a written informed consent from the patient. Three more infusions had to be administered till the end of pregnancy due to her relapsing clinical findings. She gave birth to a healthy baby (APGAR score: 9/10/10, weight 2.900 gr) after 39 weeks of pregnancy. Currently, the child is healthy without any untoward consequences and the patient is on remission with infliximab treatment.

Anti-TNF- $\alpha$  agents are classified as category B (animal reproduction studies did not demonstrate a risk but no controlled studies have been done on pregnant women) by Food and Drug Administration. The molecular structures of adalimumab and infliximab (chimeric IgG1 anti-TNF antibodies) and etanercept (a soluble receptor fusion protein composed of dimers with a ligand binding portion of the p75 receptor linked to the Fc portion of human IgG1), permit little placental transfer during the first trimester, but placental transfer cannot be excluded during the second and third trimesters.<sup>1</sup>

Although prematurity, tetralogy of Fallot, intestinal malrotation, hypothyroidism and complicated neo-natal course have been observed in infliximab treated patients with Crohn's disease; the overall rate of major fetal complications whether with Crohn's disease or RA, is similar to that expected in untreated populations.<sup>2</sup> On the other hand, a recent report of an incomplete VATER (vertebral anomalies, anal atresia, tracheoesophageal fistu-

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la, radial and renal anomalies) association in a child born to a woman with psoriatic arthritis treated with etanercept throughout her pregnancy is also noteworthy.<sup>3</sup>

In closing, as biological agents are increasingly being used for maintenance therapy in rheumatic diseases, there is no doubt that more women will either be healthy enough to consider conception or be inadvertently exposed to anti-TNF- $\alpha$  therapy during pregnancy. Before firm evidence of safety is attained from large registries, the decision to use these agents during pregnancy would better be made on case-by-case basis. Last but not least, reminding of the possible beneficial effect of TNF- $\alpha$  lowering also in infertility, it seems likely that the mounting discussion will go beyond pregnancy.

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