Infertility treatments may significantly increase multiple sclerosis activity

October 3 2012

Researchers in Argentina report that women with multiple sclerosis (MS) who undergo assisted reproduction technology (ART) infertility treatment are at risk for increased disease activity. Study findings published in *Annals of Neurology*, a journal of the American Neurological Association and Child Neurology Society, suggest reproductive hormones contribute to regulation of immune responses in autoimmune diseases such as MS.

According to a 2006 report from the World Health Organization (WHO), MS affects 2.5 million individuals worldwide and is more common among women than men. While previous research found that up to 20% of couples in Western countries experience infertility, women with MS typically do not have diminished fertility except in those treated with cyclophosphamide or high-dose corticosteroids. Medical evidence shows sex hormones and those involved in ovulation (gonadotrophin-releasing hormone (GnRH)) play an important role in the development of autoimmune disorders.

"When MS and infertility coincide, patients seek ART to achieve pregnancy," explains Dr. Jorge Correale with the Raúl Carrea Institute for Neurological Research in Buenos Aires. "Given the role of some reproductive hormones in autoimmune diseases, those with MS receiving infertility treatments are at particular risk of exacerbating their disease."

To further understand the impact of infertility treatment on MS disease activity, researchers analyzed clinical, radiological, and immune

response data in 16 MS patients who were subject to 26 ART cycles. The team recruited 15 healthy volunteers and 15 MS patients in remission not receiving ART to serve as controls.

Results show that 75% of MS patients experienced disease exacerbation following infertility treatment. MS relapses were reported in 58% of the cycles during the three month period following ART treatment. Furthermore, ART was associated with a seven-fold increase in risk of MS exacerbation and a nine-fold increase of greater MS disease activity on magnetic resonance imaging (MRI). The authors noted that 73% of exacerbations were new symptoms and 27% were attributed to a worsening of pre-existing symptoms.

Worsening was associated with three different mechanisms: 1) increase in the production of certain pro-inflammatory molecules known as cytokines (IL-8, IL-12, IFN-γ, and TGF-β by CD4+ T a GnRH-mediated effect); 2) increase in the production of antibodies against de myelin protein MOG, as well as B cell survival factor BAFF and antiapoptotic molecule Bcl-2 levels from purified B cells, these effects were a consequences of the rise of 17-β estradiol production induced by ART; and 3) authors demonstrated using an in vitro model of the blood-brain-barrier that ART facilitated the penetration of deleterious peripheral blood cells into the central nervous system, an effect mediated by the induction of the molecules IL-8, VEGF and CXCL-12.

"Our findings indicate a significant increase in MS disease activity following infertility treatment," concludes Dr. Correale. "Neurologists should be aware of possible disease exacerbation so they may discuss the benefits and risks of ART with MS patients."

More information: "Increase in Multiple Sclerosis Activity after Assisted Reproduction Technology." Jorge Correale, Mauricio F Farez, María C Ysrraelit. *Annals of Neurology*; Published Online: October 3,

2012 (DOI:10.1002/ana.23745).