To the editor:

**Important publication missing key information**

Gris and colleagues report on a randomized controlled trial comparing 100 mg aspirin to 40 mg enoxaparin started at 8 weeks gestational age in women with prior fetal loss later than 10 weeks and thrombophilia (factor V Leiden, prothrombin gene variant, protein S deficiency). The authors report an astounding 57% absolute risk reduction with enoxaparin compared with aspirin. This absolute risk reduction translates into a number needed to treat of 1.7; that is, 1.7 women with thrombophilia and a loss later than 10 weeks need to be treated with enoxaparin throughout pregnancy to prevent one fetal loss between 8 weeks and term compared with aspirin. Late fetal loss is a very common problem occurring in 2.3% of pregnancies. This dramatic finding may have a large impact on the care of women with prior late fetal loss. The case for thrombophilia screening and prophylaxis of these women is strengthened.

However, the authors, the editors, and the reviewers of this article failed to ensure that essential information was included in the article that would permit the reader to determine the strength of the internal and external validity of the study. Table 1 fails to display baseline characteristics according to treatment groups (aspirin versus enoxaparin) as is suggested in the Consolidated Standards of Reporting Trials (CONSORT) guidelines. By failing to display this information, the reader is unable to determine whether known and important prognostic factors (eg, maternal age) were equally balanced between the treatment groups. The absence of a figure to display flow of trial participants as suggested by the CONSORT guidelines does not permit the reader to determine generalizability of the findings and assess important internal validity issues. When were these patients recruited (ie, over what time frame)? Where and how were patients screened for enrollment? How many screened patients were excluded and for what reasons? How many consenting patients received the intended treatment (ie, treatment as allocated by randomization)? The method of allocation concealment was not described. How many complied completely with the intended treatment? How many were lost to follow-up? How many were analyzed for the primary outcome? Was the analysis done by intention to treat? Were there any interim analyses?

By not reporting these important study characteristics we cannot be reassured that bias is not driving these dramatic results, nor can we be sure that these results apply to our patients.

The authors should be congratulated on completing this study. Performing drug intervention trials in pregnancy is extremely challenging, fraught with medicolegal challenges, regulatory hurdles, and an absence of interest from the pharmaceutical industry. However, prior to adoption of this study’s findings, this important information needs to be revealed.

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**References**


Response:

**Thromboprophylaxis for first fetal loss**

We would like to thank Dr Rodger for his comments on our study, a nested trial in the case-control study “NOHA big first,” the results of which are not yet published.

The aim of the Nîmes Obstetricians and Haematologists (NOHA) big first, which began on January 1, 1999, was to clarify the risk factors for a first pregnancy loss.

Obstetricians and gynecologists from the southern French region of Languedoc sent us patients who experienced a pregnancy loss during their first or second pregnancy. Our multidisciplinary staff selected these cases of unexplained pregnancy loss, and 97.8% of them were investigated at the outpatient department of hematology. Patients with an obvious medical etiologic factor (1.15%) or thromboembolic antecedents (3.4%) were excluded, and 98.8% of the residual patients agreed to join the case-control study (n = 3496). There were 186 patients who were heterozygous for the factor V Leiden mutation (FVL), 127 for the prothrombin 20210G>A mutation (F2M), and 31 with a protein S insufficiency (PS). Of them, 69% (who were negative for classical antiphospholipid antibodies and hyperhomocysteinemia) were potentially eligible for our therapeutic trial (FVL: n = 127; F2M: n = 85; PS: n = 25; total: n = 237).

The therapeutic trial began January 1, 2001, and ran until January 1, 2003. Participation in this trial was proposed to the aforesaid patients with pregnancy loss from the 10th week (n = 94)
Fatal case of protothecosis in a hematopoietic stem cell transplant recipient after infliximab treatment for graft-versus-host disease

Two studies recently published in Blood have demonstrated that administration of the anti–tumor necrosis factor antibody infliximab to patients with severe graft-versus-host disease (GVHD) is associated with a high risk of subsequent invasive fungal infections.\(^1,2\) We would like to describe an unusual case of disseminated algae infection occurring in a stem cell transplant (SCT) recipient following treatment with infliximab.

A 56-year-old man 562 days after a matched unrelated donor stem cell transplantation was hospitalized for fatigue, rash, and jaundice. He previously had been diagnosed with extensive GVHD of the skin and liver and was receiving prednisone, cyclosporine A, and mycophenolate mofetil. Upon examination, the patient was jaundiced and had multiple pinkish papules on his extremities. Laboratory evaluation showed elevated liver transaminases, significant hyperbilirubinemia, and hyperglycemia. A biopsy of the skin lesions and liver was consistent with GVHD. The patient was treated with a methylprednisolone dose of 2 mg/kg per day, infliximab, and extracorporeal photopheresis. Then, 2 weeks later, he became lethargic and developed multiorgan failure and died after 5 weeks of hospitalization.

Prototheca is an achlorophyllic algae that is ubiquitous in nature.\(^1\) More than 100 human infections have been reported, most commonly involving skin and soft tissues followed by olecranon bursitis, peritonitis, cholangitis, meningitis, and bloodstream infections.\(^1,4,5\) The great majority of cases have been associated with an underlying immune deficiency.\(^5,8-11\) Treatment of protothecosis involves medical and surgical approaches.\(^3\) Results of sensitivity testing indicate Prototheca is susceptible to AMB.\(^3,5\) The utility of the azoles is questionable as most treatment failures have been associated with their use.\(^3,5\)

This is the first case of disseminated protothecosis at our institution and the first report of a very aggressive course of human protothecosis. The infection developed 2 weeks after starting infliximab treatment for GVHD. Infliximab has been associated with reactivation of latent tuberculosis in patients treated for rheumatoid arthritis and Crohn disease. Moreover, increased rates of non-Candida invasive fungal infections in hematopoietic SCT (HSCT) recipients treated with infliximab for GVHD were recently reported.\(^1,5\) The source of the infection in our patient was unclear. Most protothecal infections are attributed to local inoculation at sites of skin defects or trauma.\(^6,10\) The patient had a polymicrobial infection with *K pneumoniae* and *P wickerhamii*. It seems likely that the patient was colonized with *P wickerhamii* on the skin or in the colon, and that infliximab facilitated infection dissemination. Our patient had persistent algaemia despite 4 days of treatment with AMB. He eventually died from multiorgan failure. No previous cases of failure with AMB are reported. The cause of treatment failure was most likely due to a combination of profound immunosuppression and widespread infection.

In conclusion, human protothecosis is a rare disease, but can cause aggressive and fatal infections especially in severely immunosuppressed patients. The use of infliximab to treat steroid-refractory GVHD likely played a role in this case, and it may be wise to use it with great caution in these patients.

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