Post-partum acquired haemophilia after IVF without recurrence during a second pregnancy obtained by IVF

Sir,

We were highly interested in the case report published by Nakauchi-Tanaka et al. (2003), reporting a factor VIII inhibitor in ovarian hyperstimulation syndrome (OHSS).

Briefly, acquired haemophilia is a rare disease most often due to the development of autoantibodies directed against factor VIII that interfere with its coagulant function. The incidence is about 1 per million persons per year. Acquired haemophilia may occur in association with autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis, neoplastic diseases, drug hypersensitivity and pregnancy. However, 50% of the cases remain idiopathic. Post-partum factor VIII inhibitors most often disappear spontaneously, but the bleeding risk persists for months or years until normalisation of factor VIII (Baudo and de Cataldo, 2003).

Here, we report a patient with a pregnancy obtained by stimulation and IVF complicated by OHSS, who peripartally developed an acquired haemophilia due to factor VIII inhibitor. Interestingly, the patient did not experience a factor VIII inhibitor relapse after a second ovarian stimulation despite modest OHSS and successful IVF with an uneventful pregnancy and uncomplicated delivery.

In 1999, a 32-year-old woman with a history of infertility secondary to tubal obstruction received her first cycle of conventional stimulation for IVF. A total of 30 oocytes could be aspirated by standard transvaginal ultrasound guided procedure. The patient developed an OHSS grade III two days later with acute abdominal pain, vomiting and ascites. Three fertilized eggs were transferred into the uterine cavity despite OHSS, which later resolved. The pregnancy test became positive and an uneventful pregnancy ensued. At week 39 of the pregnancy, a healthy child was delivered by Caesarean section for breech presentation. During pregnancy, active partial thromboplastin time (aPTT) was reported normal and was prolonged at 48 s (normal range 28–38 s) on the day of delivery. Three days later, a large haematoma developed in the abdominal wall and the small pelvis necessitating transfusion of two units of red blood cells and surgical revision. Additionally, fresh frozen plasma was administered. The aPTT prolongation rose to 72 s and the patient was transferred to our institution. A total of 2000 units of Haemate® HS were administered by the attending physician empirically after taking blood samples for detailed laboratory workup.

Those further coagulation studies showed the following results (normal ranges in parentheses): aPTT 71 s (28–38), international normalised ratio (INR) 0.88 (0.7–1), factor VIII 7% (mean ~200% during late pregnancy), factor IX 137% (70–130) and ristocetin cofactor 123% (70–130). Inhibition of factor VIII was measured at 15.5 units in a modified Bethesda test (a test to detect a clotting inhibitor, normal value = 0). The haemorrhage stopped with residual factor VIII activity above 5%. Therefore, we adopted a “watchful waiting” strategy. Three weeks later, the factor VIII activity dropped to 5% and the patient developed swelling of the right ankle suggestive of haematoma. The modified Bethesda test rose to 36 units. Therefore, therapy with steroids (prednisone 100 mg daily) and infusion of 30 g immunoglobulins for 5 days were initiated. No further complications occurred and the steroid treatment could be tapered off over the following 6 months. The time course of aPTT, factor VIII and modified Bethesda test showed progressive normalisation as seen in Fig. 1.

In 2003, the patient decided to have two further embryo transfers using cryopreserved oocytes. Since these two transfers did not result in a pregnancy, a new ovarian stimulation regimen was initiated. After standard stimulation with recombinant gonadotrophins, 23 oocytes could be aspirated by conventional transvaginal technique and 2 fertilized eggs were transferred in the uterus 2 days later. A modest OHSS was again observed. The implantation was successful and the pregnancy was uneventful. After transvaginal delivery at week 39, no bleeding complications occurred. The child was in good health. Factor VIII and aPTT remained within normal ranges during the entire pregnancy and in the post-partum period.

Acquired haemophilia due to factor VIII inhibitors remains a very rare and severe complication in the post-partum period (Baudo and de Cataldo, 2003). In the presented case, the factor VIII inhibitor became clinically apparent post-partum. The pregnancy was induced by ovarian stimulation and IVF complicated by OHSS. The association between factor VIII inhibitor and OHSS has been published recently in this journal (Nakauchi-Tanaka et al., 2003). In our patient, the occurrence of the OHSS and the acquired haemophilia were
distant in time, thus, a link is only hypothetical. To the best of our knowledge, no cases of post-partum inhibitors of coagulation have been described after IVF. The treatment strategy in this case was watchful waiting initially, but when additional bleeding complications occurred and the Bethesda test showed an increase, steroids and immunoglobulins were administered successfully. These treatment options are controversial due to a lack of randomised studies. A review of the literature shows a potential benefit of immunosuppressive drugs which may shorten the time to remission, but no advantage for steroids (Hauser et al., 1995). The usefulness of high-dose intravenous immunoglobulins has been proven beneficial in a randomised trial (Schwartz et al., 1995). A novel treatment option for severe bleeding in acquired haemophilia is activated factor VII (Depka, 2002).

In general, no recurrence of acquired haemophilia has been found in subsequent pregnancies after a first episode (Michiels, 2000). However, there have been no previous reports about the risk of relapse of factor VIII inhibitors after a pregnancy obtained by IVF and complicated by OHSS. Thus, no concise information could be given to the patient about the potential harmful bleeding risk related to a new IVF procedure and a further pregnancy.

In addition to the information provided in the case report by Nakauchi-Tanaka et al. (2003), we observed a post-partum acquired haemophilia after IVF without recurrence during a second pregnancy obtained by IVF.

References


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doi:10.1093/humrep/dem121
Advance Access publication on May 18, 2007

Paternal age and birth defects: how strong is the association

Sir,

Yang et al. (2006) examined the association of paternal age and birth defects, one of which was Down syndrome, using a cohort of over 5 million subjects. They adjusted for maternal age in 10-year age bands and reported that advanced paternal age was associated with increased risks of Down syndrome. This result is almost certainly subject to residual confounding by maternal age. Kazaura and Lie (2002) demonstrated that when adjusting for maternal age using categories of 5-year intervals, residual confounding still resulted in a strong effect of paternal age (overall $P$-value for father’s age 0.006), but when the effect of maternal age was well captured, the estimated effect of paternal age was weak ($P = 0.076$). Yang et al. do acknowledge that the ‘results should be interpreted with caution for specific categories of birth defects’, but do not highlight the particular problems with their analysis of Down syndrome.

The association of many other anomalies with maternal age is less well known than that with Down syndrome so residual