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Acquired haemophilia A in women postpartum: management of bleeding episodes and natural history of the factor VIII inhibitor

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Abstract: The present study reports on the treatment of bleeding episodes and the natural history of factor VIII inhibitors in 4 patients with acquired haemophilia A postpartum. Low titre type II factor VIII inhibitors in 3 patients and high titre type I inhibitor in 1 patient became apparent immediately to 7 months after delivery. High dose human factor VIII concentrate substitution was effective in controlling bleeding episodes in two cases of factor VIII inhibitor type II, but ineffective in 1 patient with high titre type I factor VIII inhibitor. High dose gammaglobulin intravenously in 1 patient with type II factor VIII inhibitor induced a partial correction of factor VIIIc levels for 2 wk. Immunosuppressive treatment in all 4 patients with acquired haemophilia A postpartum did not reduce the potency of the factor VIII inhibitors. The low titre type II inhibitors spontaneously disappeared in all 3 patients within a few months to 1 yr after discontinuation of the immunosuppressive treatment. The high titre type I factor VIII inhibitor persisted for more than 24 yr. We conclude that immunosuppression in 4 women with acquired haemophilia A postpartum did not significantly affect the factor VIII inhibitor titre.

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Introduction

The clinical suspicion of acquired haemophilia A usually arises in elderly patients, who develop spontaneous soft tissue bleeding and bruising, haemarthros and/or gastrointestinal bleeding (1). Laboratory investigations characteristically show a prolonged APTT and a reduced factor VIII level due to an inhibitory antibody against factor VIII coagulant activity (VIIIc). Acquired haemophilia A due to an inhibitor against factor VIIIc in healthy young woman postpartum is rare (2, 3). The present study reports on the efficacy of high dose factor VIII on bleeding symptoms and the inefficacy of immunosuppression on the factor VIII inhibitor titre in 4 cases of acquired haemophilia A postpartum. Our results are discussed in view of the literature on acquired haemophilia A postpartum (1-9).

Methods

Coagulation tests were performed using routine procedures. Factor VIII coagulant activity (VIIIc) was assayed by means of the Automatic Coagulation Laboratory (ACL; Instrumental Laboratory, IJsselstein, The Netherlands) using factor VIIIc deficient plasma (Ortho Diagnostic Systems, Beersse, Belgium).

The potency of inhibitor activity against factor VIIIc was assayed in mixtures of the patient's plasma undiluted or diluted with Michaelis buffer (pH 7.42) and pooled normal plasma or porcine factor VIII (Hyate : C, Speywood Pharmaceuticals, Berkshire, England) and expressed in Bethesda Units (BU) (4). The inhibitors were classified as type I or type II following the criteria of Biggs *et al.* (5, 6) and Gawryl & Hoyer (7).

Table 1. Laboratory characteristics and final outcome in 4 cases of acquired haemophilia postpartum

	Age of patient years	Number of pregnancies prior to symptoms	Time since last delivery at onset of bleeding	F.VIIIc U/ml	Inhibitor titre Bethesda units	Outcome	Time lapse between onset bleeding and outcome	Subsequent pregnancies
Case 1	37	1	4 months	0.02	7.9	Spontaneous remission?	2 months	No
Case 2	22	3	7 months	0.01-0.02	12	Spontaneous remission	10 months	Yes, in remission, no recurrence
Case 3	31	2	2 months	<0.01	24	Spontaneous remission	28 months	No
Case 4	24	2	0	<0.01	295-625	No remission	>24 years	No

Results

Laboratory findings

The laboratory characteristics and final outcome in 4 cases of acquired haemophilia postpartum are summarized in Table 1. The inhibitors against factor VIII could be characterized as low titre type II in 3 cases and high titre type I in case 4. The type II inhibitor of case 3 did not cross-react with porcine factor VIII, Hyate-C. The type I inhibitor of case 4 cross-reacted with porcine factor VIII, Hyate : C (22 BU). The type II inhibitors of cases 1 and 2 were not tested against porcine factor VIII.

Clinical observations

Case 1 presented in February 1990 with bruises and ecchymoses. Continuous factor VIII (Factor VIII CPS, Central Laboratory Bloodtransfusion, Amsterdam) infusion for the treatment of haemarthros and bruises was clinically effective and treatment with prednisone 1 mg/kg was started (Fig. 1). The factor VIII inhibitor disappeared 2 months after diagnosis while still on prednisone treatment 20 mg/d (Fig. 1) and did not recur during a follow-up period of 5 yr.

Case 2 presented in September 1990 with bleeding after tooth extraction and menorrhagia 7 months postpartum. Cyclophosphamide 100 mg/d (0.7 mg/kg/d) for 1 month did not affect the factor VIII inhibitor titre and factor VIIIc levels. The inhibitor against factor VIII spontaneously disappeared several months after discontinuation of cyclophosphamide (Fig. 2). A fourth pregnancy in 1992 was uneventful with no recurrence of an inhibitor against factor VIII.

Case 3 presented in June 1991 with muscle and soft tissue bleedings, menorrhagia, bruises and haemarthros. A single dose of 4000 U human factor VIII (Hemophil-M Baxter, Hyland Division, Lessines,

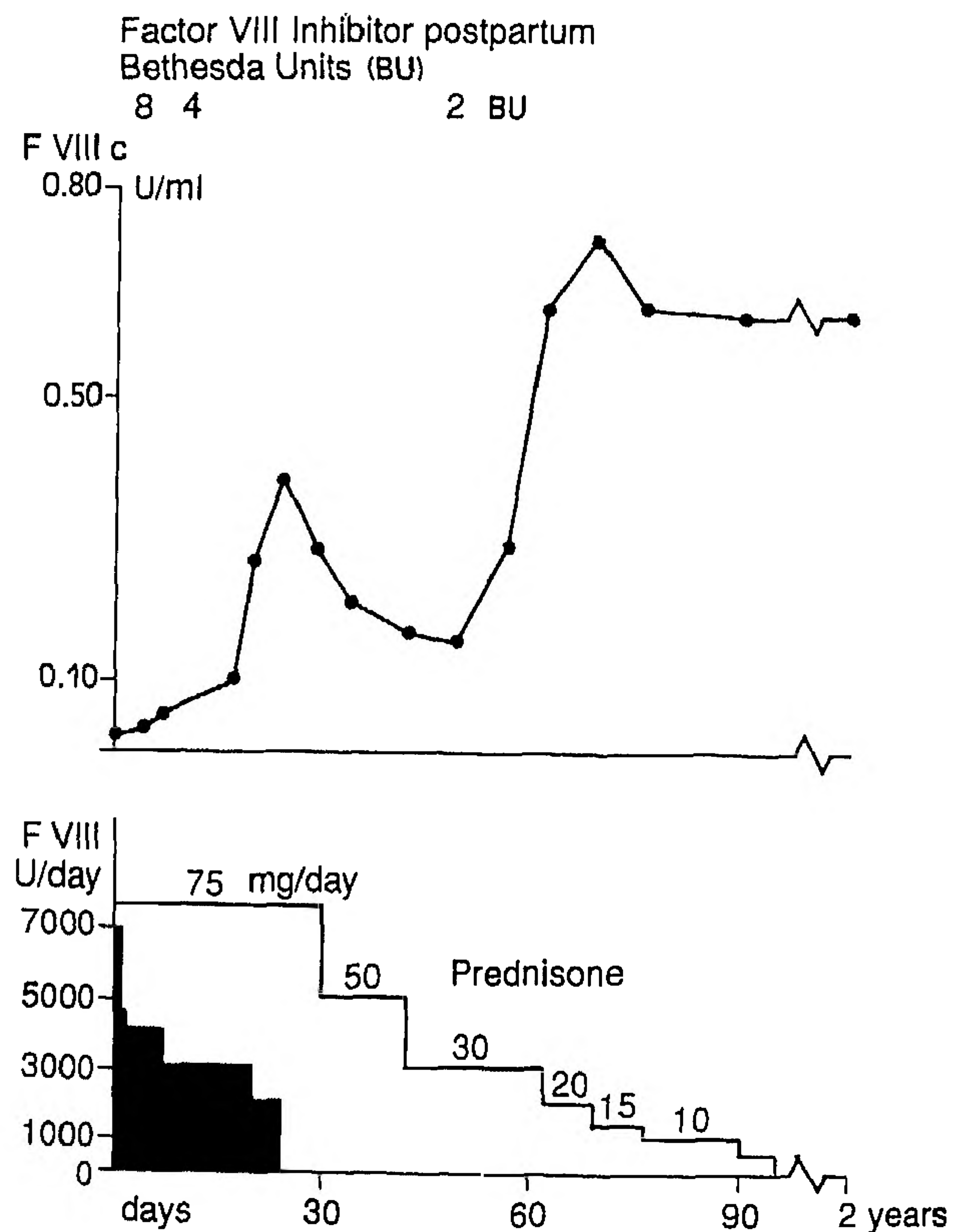


Fig. 1. Factor VIII substitution and prednisone treatment in relation to factor VIIIc and factor VIII inhibitor levels in patient 1 with acquired haemophilia A postpartum.

Belgium) corrected the prolonged APTT due to a rise of factor VIIIc from <0.01 U/ml to 0.36 U/ml (Fig. 3), which was followed by a curvilinear disappearance of factor VIIIc from the circulation to 0.10 U/ml at 6 h postinfusion. Treatment of major bleeding from haemorrhoides with Hemophil-M was effective and resulted in normal factor VIIIc levels with the disappearance of the factor VIII inhibitor (Fig. 3). Concomitantly, treatment was started with prednisone 1 mg/kg/d for 6 wk followed by cyclophosphamide 2 mg/kg/d from the 3rd to 6th week of prednisone treatment (Fig. 3). The inhibitor

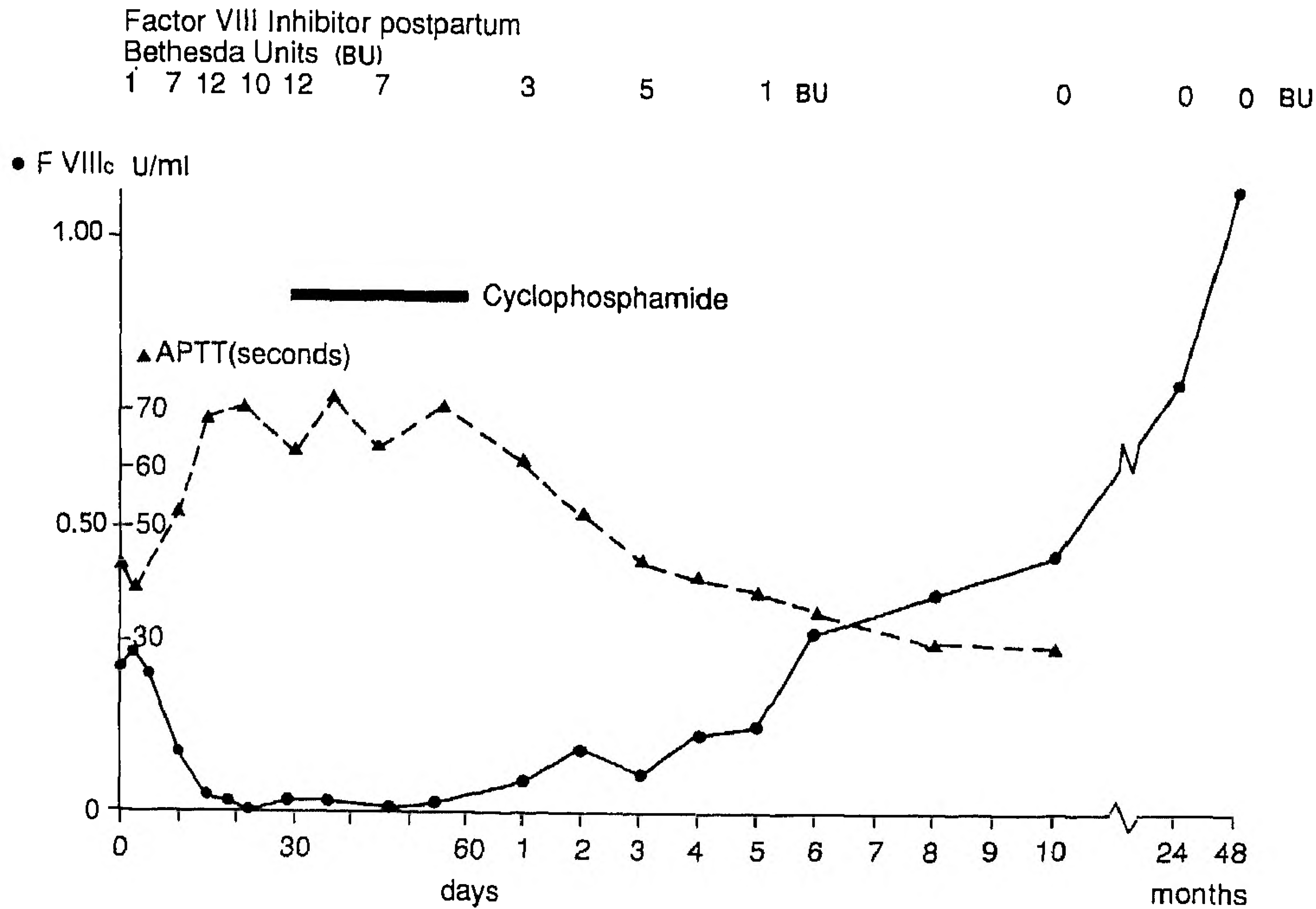


Fig. 2. No effect of cyclophosphamide treatment on the activated partial thromboplastin time (APTT), and factor VIIIc and factor VIII inhibitor levels in patient 2 with acquired haemophilia A postpartum.

against factor VIII reappeared after discontinuation of factor VIII substitution and immunosuppression. Subsequently, high dose gamma-globulin 0.5 g/kg/d for 5 d resulted in a transient decrease of the inhibitor titre and factor VIIIc levels of sufficient haemostatic potency for 2–3 wk (Fig. 4).

Case 4 the second pregnancy of a 24-yr-old woman in January 1972 was complicated by hypovolaemic shock and the birth of a lifeless child by Caesarian section under the cover of 32 units of blood in the postpartum period. The excessive bleedings were due to acquired haemophilia A (Table 1).

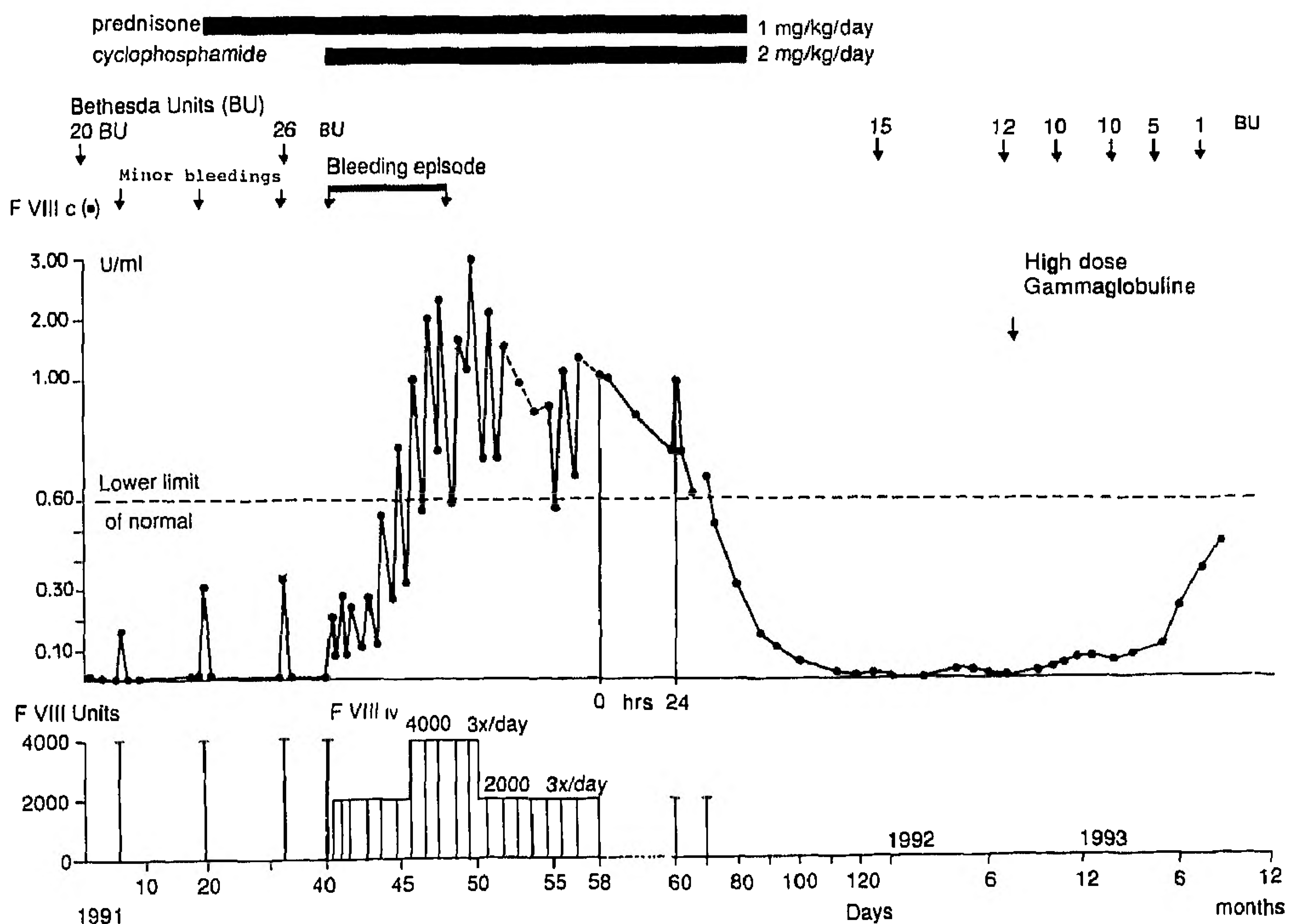


Fig. 3. Effectiveness of factor VIII substitution and ineffectiveness of prednisone/cyclophosphamide treatment in patient 3 with acquired haemophilia A postpartum.

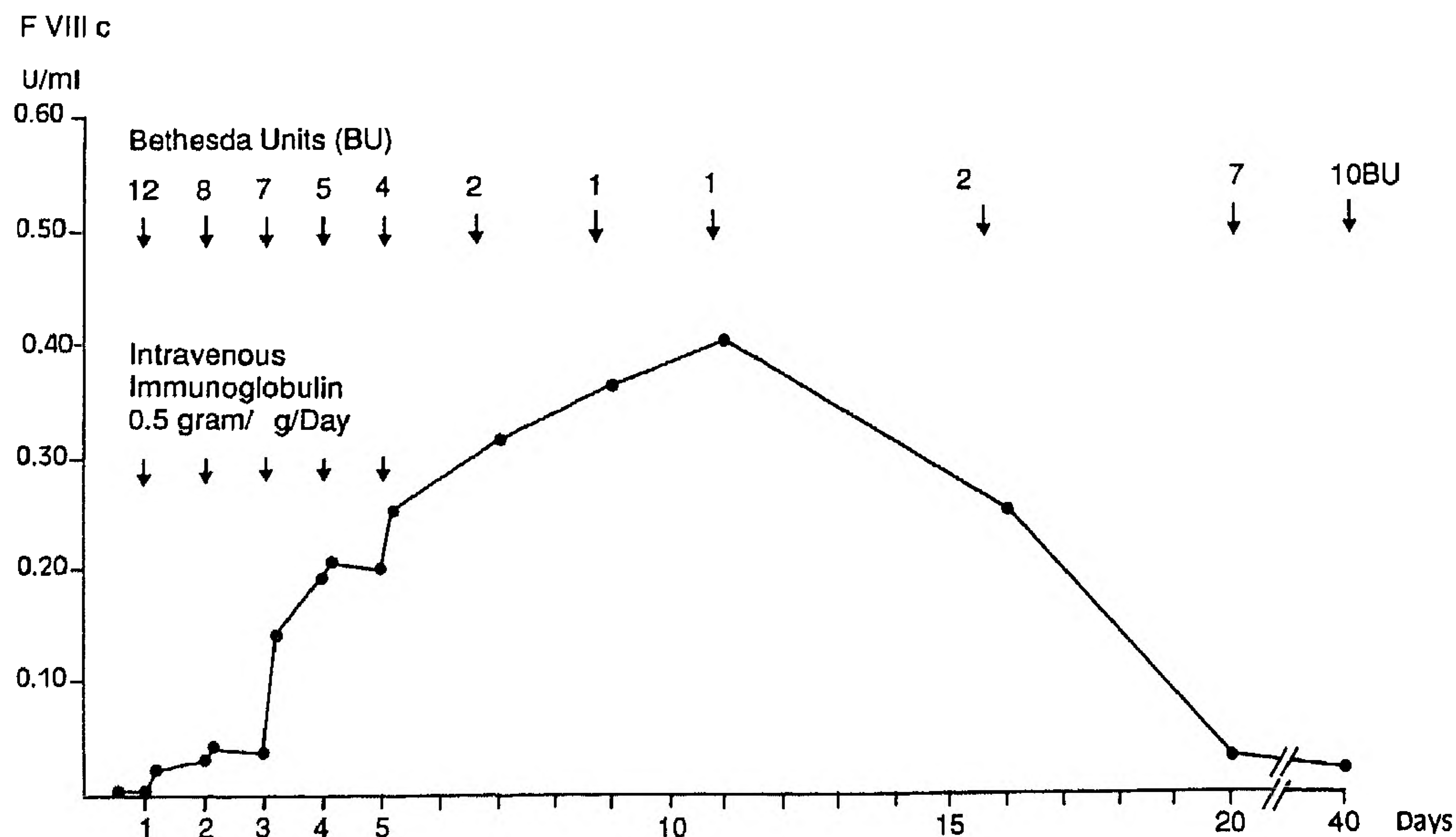


Fig. 4. The effect of intravenous gammaglobulin on factor VIIIc and factor VIII inhibitor levels in patient 3 with acquired haemophilia A postpartum (see Fig. 3).

Prednisone 1 mg/kg for 3 wk and tapering off the dose within 5 months was ineffective. In 1977 the inhibitor potency was 600 BU. Factor VIII levels remained <1% even after transfusion of 10,000 U cryoprecipitate for the treatment of severe haemarthros of the left knee. Recurrent joint bleedings led to severe arthropathy of the knee joints. The factor VIII inhibitor persisted (625 BU in 1984 and 420 BU in 1988) and completely inhibited human factor VIIIc both *in vivo* and *in vitro*, which is consistent with a type I factor VIII inhibitor.

Discussion

Treatment of bleeding symptoms in acquired haemophilia A should be based upon the clinical circumstances and the inhibitor characteristics in the Bethesda assay (10, 11). Success with factor VIII concentrate depends on both the type and potency of the inhibitor. The potency of the factor VIII inhibitor in women postpartum is usually low. A non-linear type II factor VIIIc inactivation is usually seen in women with acquired haemophilia postpartum (2). Type II antibodies do not completely inactivate factor VIIIc even when tested undiluted (5, 6). Therefore, it is not necessary to neutralize the inhibitor completely in order to obtain *in vivo* factor VIIIc levels of sufficient haemostatic potency (2, 7). High dose human factor VIII substitution in the emergency situation of major bleeding in case 3 with type II factor VIII inhibitor resulted in correction of factor VIII levels and disappearance of the inhibitor as long as the substitution therapy was continued.

DDAVP intravenously will be of no clinical use in controlling bleedings, because it induces no or slight increase of factor VIIIc, which is rapidly inactivated by the factor VIII inhibitor. In case 3, high-dose immunoglobulin in standard dosages (0.5 g/kg for 5 d) was transiently effective and no cross reactivity of the inhibitor to porcine factor VIIIc was demonstrated retrospectively (10, 11). Therefore, high dose immunoglobulin intravenously as well as substitution with porcine factor VIII (Hyate : C) might have been a better alternative and even more effective than human factor VIII to arrest bleedings in this case.

The high titre type I factor VIII antibodies persisted for more than 24 yr in case 4 and cross-reacted with porcine factor VIII, Hyate : C. Such high titre type I factor VIII inhibitors do not respond to human and porcine factor VIII substitutions and have a high risk of life-threatening bleeding complications, which should be treated preferentially with recombinant factor VII or alternatively with FEIBA (10, 11).

Postpartum factor VIII inhibitors usually persist for a few months to several years (2). The final outcome of postpartum inhibitors is favorable with a probability of spontaneous disappearance of the inhibitor of almost 100% at 30 months (2, 3). A second pregnancy in documented patients with prior postpartum factor VIII inhibitors did not cause a reappearance of the factor VIII inhibitor (2, 3, 8, 9) (case 2, Table 1).

The effect of immunosuppressive treatment on the natural history of factor VIII inhibitors in women postpartum is questionable. In a retro-

spective analysis of 51 postpartum factor VIII inhibitor patients, steroid treatment is not superior to no treatment and immunosuppression did not induce a complete remission, but may have slightly reduced the time to complete remission. The time to the disappearance of the factor VIII inhibitor was 8 months in 18 patients with immunosuppressive treatment, 12 months in 23 patients with steroid treatment and 16 months in 10 patients without steroids or immunosuppressive treatment (3).

The present study extends our original observations in 1978 (2) and the findings derived from the literature (2, 3), that there is no evidence for the benefit of immunosuppressive treatment in young women with acquired haemophilia A postpartum. In contrast, immunosuppression is a first-choice treatment in acquired haemophilia A affecting elderly patients, because it induces a transient or persistent disappearance of the inhibitory auto-antibodies against factor VIII in the majority of these cases (12).

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