Pregnancy and antibody to factor VIII

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SUMMARY A patient who had developed a factor VIII antibody three weeks after the birth of her first baby became pregnant for the second time 10 weeks later. The pregnancy was normal apart from extensive spontaneous bruising during the first two months. This bleeding tendency disappeared in the third month of gestation and the antibody became undetectable during the eighth month. It had not reappeared seven months later. An unexplained long bleeding time and low platelet count were noted during the last trimester. The literature on postpartum coagulation inhibitors is reviewed.

Factor VIII antibody is a rare cause of haemorrhage in previously healthy postpartum women. Women who may have had this type of haemorrhagic disorder were reported by Rosenthal *et al.* (1937) and by Madison and Quick (1945). The nature of the defect was first reported in 1946 when the plasma of two such patients was shown not only to resemble haemophilic plasma but to have an inhibitory effect on normal clotting (Fantl and Nance, 1946; Chargaff and West, 1946). Dreskin and Rosenthal (1950) and Frick (1953), studying similar postpartum inhibitors, demonstrated that they were directed against antihaemophilic factor. Shapiro (1967) and Robboy *et al.* (1970) showed that these inhibitors were immunoglobulins as are the factor VIII antibodies found in treated haemophiliacs (Leitner *et al.*, 1963).

We describe a patient with a postpartum factor VIII inhibitor who became pregnant again at a time when her factor VIII level was extremely low and while haemorrhagic manifestations were still present.

Case report

A previously healthy 33-year-old Caucasian woman with no family history of abnormal bleeding developed spontaneous bruises 20 days after her first child was born. The pregnancy had been normal but Kielland forceps delivery was necessary for delay in the second stage and was followed by a self-limiting haemorrhage of approximately 500 ml. On the fifth day there was a further brisk haemorrhage, and retained products of conception were removed by curettage. Bleeding then ceased and blood transfusion was not necessary.

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Twenty days after delivery large spontaneous bruises began to appear on the arms and legs and similar bruises continued to develop for the next four months. Slight bleeding from the gums was noticed several times but there were no haemarthroses nor haemorrhages from any other site. The baby was completely normal and breast feeding continued for four months.

Ten weeks after the spontaneous bruising had appeared the patient became pregnant again. No vaginal blood loss was noticed but bruises continued to develop during the first two months of pregnancy. No attempt was made to treat her with blood products, steroids or other immunosuppressives. During the third month all clinical evidence of a bleeding tendency disappeared, and the pregnancy progressed normally. Labour was induced at 39 weeks' gestation and the birth of the second baby was uncomplicated. Postpartum blood loss was normal and during the nine months after the birth there were no signs of bleeding in mother or baby.

Methods

Factor VIII coagulant activity (VIII:C) was measured by the two-stage technique of Biggs and Douglas (1953) and antibody to factor VIII by the method of Biggs and Bidwell (1959). Platelet counts were performed manually and the bleeding time was measured by Ivy's method. Platelet aggregation was performed on fresh platelet-rich plasma in a Born-Michal aggregometer and platelet retention by Bowie's method with glass bead columns (Bowie *et al.*, 1969). Von Willebrand factor (VIII:WF) was assayed by the method of Weiss *et al.* (1973). Factor VIII related antigen (VIII:AG) was determined by immunoelectrophoresis (Laurell,

1966). Platelet-bound IgG and serum anti-platelet antibody were tested by a quantitative complement lysis inhibition assay (Dixon *et al.*, 1975) and anti-platelet agglutinins by a modification of the method of Dausset (1954).

Results

Factor VIII:C, factor VIII antibody levels, platelet counts, and bleeding times during and after the second pregnancy are shown in the Figure.

Immediately after the second baby was born the factor VIII:C level of the mother was 92 IU/dl and antibody to factor VIII was not detectable. In the postnatal period the mother's factor VIII:C fell to just below normal but antibody to factor VIII did not reappear, and the factor VIII:C

returned to normal by the eighth week post partum (Figure); it was still normal five months later. The baby's factor VIII:C at birth was 37 IU/dl (cord blood) but rose to 54 IU/dl by the ninth day and was 58 IU/dl seven months later. No antibody to factor VIII was detectable, and the results of other coagulation tests remained within normal limits for her age.

Factor VIII:R:AG was 200% at 29 weeks' gestation. It remained above 200% (normal for pregnancy) throughout the last trimester and had fallen to 114% (normal 50-150%) by seven months post partum.

Platelet aggregation with ADP, adrenaline, ristocetin, and collagen was normal in tests done from 29 weeks to term, and VIII:WF was normal at 32 weeks' gestation. However, platelet retention by glass beads (normal range 40-90%) was very much reduced (0%, 17%, 5%) at 32, 34, and 39 weeks.

Figure Factor VIII: C and factor VIII antibody levels, bleeding times, and platelet counts during and after the second pregnancy.

Platelet-bound IgG was normal and serum anti-platelet IgG was not detected at 34 weeks or at term. Platelet agglutinins were not present at 34 weeks.

Further investigations at the time of the coagulation abnormality failed to establish any other pathology. Haemoglobin and white cell count remained normal, blood chemistry and liver function were normal, antinuclear factor and other auto-antibodies were not present.

Discussion

There have been approximately 30 case reports of postpartum coagulation defects of this type. These are listed in the Table. Nearly all the inhibitors tested were found to be directed against factor VIII. Only two were found to be anti-factor IX antibodies (Marmont *et al.*, 1969; Özsoylu and Özer, 1973). The antibody was usually detected within a few months of the delivery and disappeared spontaneously after a variable time, ranging from four months to more than 10 years. There is only one report of a patient developing a factor VIII antibody for the first time during pregnancy rather than in the postpartum period (Marengo-Rowe

et al., 1972). In most cases pregnancy and delivery were quite normal and the patients had been completely healthy. However, three patients had some evidence of an auto-immune disorder before the development of the inhibitor (Barkhan, 1952; Robboy *et al.*, 1970).

Clinical features differ slightly from those of haemophilia in that large ecchymoses, muscle bleeds, haematuria, menorrhagia, and retroperitoneal bleeds are more common than haemarthroses and may be fatal (Table).

There are four reports of postpartum women with factor VIII inhibitors in which further pregnancies are mentioned. In three of these (Hewlett and Haden, 1949; Conley *et al.*, 1950; Margolius *et al.*, 1961) there was some evidence of a continuing bleeding tendency during and after the subsequent pregnancy. In the fourth (Frick, 1953), the severity of the bleeding increased during the subsequent pregnancy. Conversely, our patient went into remission during her second pregnancy, indicating that pregnancy does not necessarily affect the natural progress of the disorder.

The babies born to mothers with pre-existing coagulation defects have all been clinically normal although in two cases the mothers were known to

Table Reported cases of postpartum coagulation defects due to factor VIII inhibitors§

Author		Age of patient (years)	Number of pregnancies prior to symptoms	Time since last delivery at onset of symptoms	Outcome
Rosenthal <i>et al.</i> †	1937	28	Not stated	3 years	Complete recovery after 13 years
Madison and Quick	1945	29	3	17 months	Died (respiratory obstruction due to haemorrhage)
Chargaff and West‡	1946	30	1	4 months	Complete recovery after 11 years
Fantl and Nance	1946				
Heinle <i>et al.</i>	1949	33	1	12 months	{ Clinical recovery after 6 years Laboratory tests normal after 10 years
Hewlett and Haden	1949				
Hewlett and Haden	1949	40	5 + 1*	3 months	Complete recovery within 2 years
Dreskin and Rosenthal	1950	30	1	4 months	Clinical recovery after 13 months
Conley <i>et al.</i> ‡	1950	30	1 + 3*	Immediate	Continued for at least 7 years
Barkhan	1952	26	0 + 3*	Not stated	Not stated
Biggs and Macfarlane	1953	35	2	8 months	Continued for at least 6 months
Frick	1953	24	1	3 months	Complete recovery after 2½ years
O'Brien	1954	35	1	3 months	Complete recovery after 4 months
Bruno and Brody	1954	27	1	3 months	Not stated
Torregrosa <i>et al.</i>	1954	36	1	3 weeks	Died (retroperitoneal haemorrhage)
Alexander	1955	21	1	12 days	Died (uncontrollable postpartum haemorrhage)
Nilsson <i>et al.</i>	1958	32	1	4 months	Complete recovery after 1 year
Margolius <i>et al.</i>	1961	30	7	3 months	Complete recovery within 6 years
Margolius <i>et al.</i>	1961	24	1	2 months	Clinical recovery after 8 months
Bloom <i>et al.</i>	1966	29	1	3 months	Complete recovery after 19 months
Greenwood and Rabin	1967	20	1	6 days	Clinical recovery within 3 months
Shapiro	1967	36	3	2 months	Complete recovery after 6 months
Sherman <i>et al.</i>	1969	22	Not stated	1 week	Complete recovery within 4 months
Robboy <i>et al.</i>	1970	23	2	2 months	Complete recovery within 18 months
Robboy <i>et al.</i>	1970	21	Not stated	2 months	Clinical recovery within 4 weeks
Marengo-Rowe <i>et al.</i>	1972	14	1	In pregnancy	Complete recovery within 1 year
Fox and Tilson	1974				

*Abortions †Outcome reported by Dreskin and Rosenthal (1950) ‡These two papers report the same patient

§In a few of the early reports an inhibitor was not demonstrated although the clinical and laboratory features were highly suggestive of this type of coagulation defect.

have detectable inhibitor and a clinical bleeding tendency at the time of birth (Frick, 1953; Marengo-Rowe *et al.*, 1972). The unusual case described by Frick is the only one in which the baby, though clinically normal, was born with a coagulation inhibitor corresponding exactly to that of the mother. The anticoagulant was detectable in the baby for about two and a half months. Assuming that these inhibitors are IgG antibodies, they are likely to cross the placenta and persist for several weeks in the neonate, as do anti-Rhesus or anti-viral antibodies. Although the patient described by Marengo-Rowe *et al.* had detectable factor VIII antibody at the time of birth, there was no evidence that this antibody had crossed the placenta. The baby was born prematurely with a normal level of factor VIII (80%) although the mother's level was very low (3% of normal).

In our case the baby's factor VIII was low but there was no bleeding tendency and no detectable antibody to factor VIII.

The thrombocytopenia, long bleeding time, and abnormal platelet retention in our patient were first noted in the last trimester after the titre of antibody to factor VIII had fallen and factor VIII:C was rising. They had all returned to normal by four weeks post partum. Platelet function tests were not performed earlier in the pregnancy.

Our patient had no evidence of an auto-immune disorder and, in particular, no detectable serum anti-platelet IgG or abnormal platelet surface IgG even when her platelet count was low and the platelet function abnormal. Acquired von Willebrand's disease was excluded by high VIII:R:AG, normal platelet aggregation with ristocetin, and normal VIII:WF.

The aetiology of this disorder is unknown. It is thought that the pregnant mother can be sensitised to soluble fetal plasma proteins such as the lipoprotein allotypes (Dürwald *et al.*, 1965) but there is, at present, no definite experimental evidence that factor VIII antigenic allotypes exist. If the maternal immune system is stimulated by fetal factor VIII the antibody so formed must crossreact with maternal factor VIII if the bleeding tendency is to be explained. One would expect such an antibody to reappear after some of the subsequent pregnancies, as in Rhesus sensitisation, but relapses have not been reported. The variable nature of this disorder also argues in favour of a more complex pathogenesis.

There is not only an association between factor VIII antibodies and auto-immune disorders, such as rheumatoid arthritis and systemic lupus, but also a well-known alteration of immune reactivity in normal pregnancy. These two observations suggest

that a likely explanation of postpartum factor VIII antibodies is that of a temporary breakdown in the mother's tolerance to her own factor VIII. Whether or not this is the case, this rare disorder does resemble other auto-immune states in its variable onset and duration, its varying severity, and in the fact that its aetiology is still a mystery.

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