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Congenital afibrinogenaemia and successful pregnancy outcome. Case report

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Case report

The successful outcome of pregnancy in a 25-year-old woman with congenital afibrinogenaemia is discussed. She had been found to have afibrinogenaemia soon after birth, following investigation for severe bleeding from her cord stump. She frequently suffered with severe bruising, heavy menstruation and excessive bleeding after dental treatment. She had had an average of two to three fibrinogen transfusions a year at the time of acute bleeding episodes such as following tooth extraction, appendicectomy or for a heavy period. Her first pregnancy in August 1988 miscarried at 7 weeks gestation with excessive bleeding. Her fibrinogen level was undetectable. She was transfused with fibrinogen prior to the evacuation of retained products of conception. Her second pregnancy followed soon after (March 1989), and was complicated with multiple episodes of bleeding from the 5th to 13th week, during which time she received intermittent fibrinogen transfusions.

Repeated weekly 5 gm fibrinogen transfusions from the 13th week served to halt the bleeding, but premature separation of the placenta at 27 weeks gestation resulted in preterm labour and the birth of a live 610 g baby, who died shortly afterwards. Her pre- and post-fibrinogen transfusion levels during this pregnancy varied between 1 and 100 mg/dl and the level was 0·9 mg/dl on the day of the placental abruption. After this tragic episode it was decided she should have prophylactic fibrinogen transfusions during the next pregnancy. To avoid the inconvenience of repeated hospital admissions the patient was taught to give her own fibrinogen infusions at home. She infused 5 g fibrinogen every 8–10 days at home. She conceived after about 2 months of starting this treatment and, from 7 weeks of pregnancy, she was followed up by both obstetrician and haematologist every 2 weeks and 1 week, respectively. It was decided to maintain a fibrinogen level of at least 100 mg/dl during pregnancy and 150 mg/dl during labour. This was achieved by thrice weekly infusions of 7 g of fibrinogen, increasing to 10 g as gestation increased. An extra 10 g of fibrinogen was given at the time of induction of labour.

Assessment of fetal growth and wellbeing was undertaken by repeated ultrasound and Doppler studies. As fetal growth was normal and there was no bleeding, pregnancy was continued to the 39th week of gestation. Labour was induced on 20 August 1990 using prostaglandin E_2 vaginally, artificial rupture of the membranes and oxytocin. An epidural anaesthetic was given during labour. A low cavity forceps delivery was necessary because of delayed progress in the second stage and resulted in the birth of a healthy male baby of 3550 g. The patient returned home on the third postnatal day with advice to continue fibrinogen infusions at a reduced dose of 5 g thrice weekly for a further 4 weeks. She had a normal puerperium and was completely well at 6 weeks after delivery.

Discussion

Congenital afibrinogenaemia was first described by Rabe & Solomen (1920). Since then approximately 150 cases have been reported. It is an autosomal recessive disorder affecting males and females in equal proportions.

This is the second reported case of congenital afibrinogenaemia in the world literature with a successful pregnancy outcome; and it is the first

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to end with a vaginal delivery at term. The previous successful pregnancy was managed by Inamoto *et al.* (1985) and ended in caesarean section at 37 weeks gestation.

The successful management of these two pregnancies confirms that fibrinogen is important in the maintenence of normal pregnancy. Several cases have been reported previously by various authors in which failure to complete a normal pregnancy has been ascribed to a deficiency of fibrinogen, using terms such as afibrinogenaemia (Evron *et al.* 1985); hypofibrinogenaemia (Hahn *et al.* 1978; Aznar *et al.* 1970; Pritchard 1961); dysfibrinogenaemia, or deficiency of factor XIII (fibrin stabilizing factor) necessary for cross linking of fibrin (Egbring *et al.* 1970; Fisher *et al.* 1966).

The exact role played by fibrinogen in maintaining pregnancy is not well defined but the hypothesis developed by Pritchard (1961) is attractive. He suggested that minute placental separation and haemorrhages occur in a normal pregnancy and are controlled by prompt conversion of maternal fibrinogen to fibrin. The hyperfibrinogenaemia of normal pregnancy maintains the integrity of placental implantation and in women with fibrinogen deficiency, the protection may be lacking. Leidholm *et al.* (1975) suggested that normal fibrinogen seems to play a significant role in implantation. Penn *et al.* (1971) produced a high rate of fetal absorption in animal models with hypofibrinogenaemia.

As our patient conceived easily on two occasions without the administration of fibrinogen it may be that fibrinogen is not so important during implantation but is necessary for continuation of the pregnancy. There have been no reported cases of afibrinogenaemia where the pregnancy has advanced more than a few weeks without treatment. Recurrent miscarriage with afibrinogenaemia has been described by Evron *et al.* (1985). The minimum plasma level of fibrinogen required for a successful pregnancy is not yet known. A value of 60 mg/dl has been suggested by Inamoto *et al.* (1985). The levels resulting from therapy must be high enough to prevent recurrent miscarriage (Aznar *et al.* 1970; Hahn *et al.* 1978) and premature separation of the placenta (Ness *et al.* 1983; Pritchard *et al.* 1961).

Although repeated fibrinogen/cryoprecipitate transfusions carry the risk of infection with the hepatitis B and HIV viruses and the possibility of fibrinogen antibody production, alloimmunization, uncontrollable haemorrhage at a later date and an exaggerated thrombotic response, it is the only hope of achieving a successful pregnancy. Our patient was given fibrinogen concentrate in preference to cryoprecipitate because it can be stored at room temperature and is therefore ideal for home treatment (cryoprecipitate must be stored at −20°C).

Because the half life of fibrinogen is only 48 h frequent infusion is needed. To overcome the inconvenience of frequent hospital visits our patient was trained before conception to inject her own fibrinogen at home. The fibinogen level was maintained at ≥100 mg/dl by thrice weekly infusions. Increasing amounts of fibrinogen were needed as the pregnancy progressed to maintain this level. The amount used was increased gradually from 18 g weekly in early pregnancy to 30 g weekly at term. The fibrinogen requirement falls sharply after delivery. Our patient needed only 15 g weekly to maintain the same level during the puerperium.

We feel that in the absence of associated obstetric complications it is reasonable to allow pregnancy to continue to term. Induction of labour was preferred to spontaneous onset to ensure that delivery was effected in planned conditions with the full support of the haematological team. Post partum haemorrhage is a real danger (Ratten *el al.* 1969; Strickland *et al.* 1982). According to Gilabert *et al.* (1987) a minimum fibrinogen level of 120 mg/dl is required for haemostatic protection during delivery. We gave an extra 10 gm of fibrinogen during induction to maintain a fibrinogen level above 150 mg/dl.

Epidural analgesia is possible provided normal fibrinogen levels are maintained. As the condition is an autosomal recessive the fetus is very unlikely to have a similar disorder. Vaginal delivery should be the aim but, as there is no increased risk of intracranial haemorrhage due to a bleeding diasthesis, instrumental delivery is acceptable. A high level of fibrinogen should be maintained during the puerperium as delayed post partum haemorrhage (Strickland *et al.* 1982) has been reported in a patient with hypofibrinogenaemia. Our patient continued fibrinogen therapy for 4 weeks post partum.

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