Treatment of midgestational placental haemorrhage with recombinant factor VIIa

Krafft, A; Asmis, L M; Zimmermann, R


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Midgestational placental haemorrhage threatens both mother and fetus. Reconciling maternal haemostasis with fetal well-being is a major therapeutic challenge. Between 24 and 26 weeks gestation in particular, despite aggressive obstetric and neonatal management, fetal survival is uncertain and survivor morbidity considerable (1).

Case report
A 42-year-old gravida 6 para 5 was referred at 24+5 weeks gestation for persistent vaginal haemorrhage since week 9. Admission haemoglobin (Hb) was 7.7 g/dl. Cardiovascular status was stable despite ongoing heavy bleeding; transfusion of two units of packed red blood cells increased the Hb to only 8.1 g/dl. Personal and family haemorrhagic and thromboembolic history was negative; no antiplatelet drugs had been taken (platelet count: 291 G/l). There were no risk factors for, nor a previous history of, placental abruption. Fibrinogen levels and prothrombin and activated partial thromboplastin times were normal, as were the levels of von Willebrand factor (ristocetin cofactor activity) and factor XIII (amidolytic activity). D-dimers were elevated at 1,800 ng/ml; hyperfibrinolysis was excluded (ROTEM™ analysis). Ultrasonography revealed a 71×51×85 mm retroplacental haematoma and a normal-for-dates fetus.

Given the active bleeding, immediate danger to maternal fetal well-being, absence of therapeutic alternatives, and virtual certainty of adverse fetal outcome from delivery at this gestational age, we evaluated the off-label use of human recombinant factor VIIa (rFVIIa). A literature search revealed no reports of rFVIIa use in pregnancy. We estimated the thrombotic risk attributable to rFVIIa treatment to be <3% for the mother and less for the fetus (a literature search and manufacturer’s data [NovoNordisk, Bagsvaerd, Denmark] provided no evidence that rFVIIa crossed the placenta), with a reasonable probability of successful haemostatic response. After we informed the patient of the nature of the drug, the potential complications (including thromboembolism and death), and the absence of reported experience in this indication, she signed an informed consent form. Based on an unpublished report obtained from the manufacturer of rFVIIa use (NovoSeven®, 30 µg/kg bodyweight [BW]) in a pregnant woman with congenital factor VII deficiency, and to minimise maternal thrombotic risk, we opted for a dose of 20 µg/kg BW (2.4 mg) intravenously (iv). Contractions were managed with hexoprenaline iv (Gynipral®, Nycomed, Waedenswil, Switzerland) and rFVIIa [Celestone®] 2×12 mg iv; Essex, Lucerne, Switzerland).

Active bleeding virtually ceased within hours after rFVIIa administration although old blood and blood clots continued to discharge over the following weeks at levels not requiring transfusion. The intrauterine haematoma shrank by two thirds (Fig. 1). Maternal Hb increased to 10.9 g/dl after treatment with iv iron (1,200 mg in total; Venofer®, Vifor International, St Gallen, Switzerland) and recombinant human erythropoietin (total 20,000 U; Eprex®, Janssen-Cilag, Baar, Switzerland). At 31+3 weeks gestation, premature rupture of membranes prompted antibiotic prophylaxis iv. Caesarean section the next day delivered a clinically healthy girl (1,720 g, 53rd percentile, normal umbilical pH, normal Apgar) who was admitted to neonatal intensive care for prematurity but did not require mechanical ventilation. Maternal postpartum recovery was uneventful, and the patient was discharged on day 5. We observed no side effects from rFVIIa treatment in either mother or fetus. Placental pathology confirmed the ultrasound diagnosis of partial placental abruption and revealed an old extensive retroplacental haematoma, but no signs of chorioamnionitis.

Discussion
According to a cell-based model of coagulation, factor VII plays a key role in initiating haemostasis. Administration of rFVIIa maintains haemostasis by enhancing thrombin generation, leading to the formation of a stable fibrin clot (2). Literature on the obstetric applications of rFVIIa is sparse and mainly limited to case reports and case series on the treatment of postpartum haemorrhage (3). We were aware of the difficulty of gauging thromboembolic risk in off-label patients in general and in our patient in particular. Reports of rFVIIa-related thromboembolic events have increased dramatically in recent years. O’Connell et al. reviewed 431 reports but due to data analysis deficiencies failed to provide their incidence or frequency (4). In on-label treated patients, the reported thromboembolic complication (TEC) rate is <1% versus ≥10% in off-label patients (5). Recent meta-analyses of off-label rFVIIa applications in high-risk sur-
Gical patients report TEC rates of 7.7% (n = 1,067) and 7.1% (n = 507) (6, 7), however, these figures need to be set against the basal TEC risk of 5.1% and 5.2%, respectively, in controls without rFVIIa treatment. We estimated the basal TEC risk as being clearly lower than either of these figures (between 0.1 and 0.01% per year) in our 42-year-old patient with no concomitant morbidity or medication, and a negative personal and family thromboembolic history.

Pregnancy is a prothrombotic risk state that compounds relative TEC risk five-fold (8). The overall venous thromboembolic risk associated with pregnancy, 1/1,000 to 1/2,000 deliveries (9), further supports our estimates, as does the absence of thromboembolism in the series of 79 women treated with rFVIIa for postpartum haemorrhage (3). In view of all the above, we estimated that the mother’s thrombotic risk attributable to rFVIIa treatment was <3%. To minimise this risk we opted for a low dose of rFVIIa, following Franchini et al. who reported (mostly single) doses of 16.7–48 µg/kg body weight (3). We estimated the risk to the fetus as lower still given the low probability of significant drug transfer across the placenta, based on a negative literature search and pathophysiological considerations. Earlier studies had shown no placental transfer of erythropoietin (molecular weight 30.4 kDa), a protein considerably smaller than rFVIIa (50 kDa), making it unlikely that rFVIIa could ever cross the placenta (10). Cade et al. showed that preterm neonates present low FVII levels at birth (27%) while mothers have elevated FVII levels (11).

Preterm births account for 75% of perinatal mortality and over half of long-term morbidity. Survivors are at increased risk of neuro-developmental impairment and gastrointestinal and respiratory complications (12). Prolongation of pregnancy, as in our case, from 25 to at least 32 weeks significantly lowers not only infant mortality but also morbidity (bronchopulmonary dysplasia, intraventricular haemorrhage and necrotizing enterocolitis) (13).

We conclude that rFVIIa warrants appropriate safety and efficacy studies as a treatment option of last resort for maternal-fetal haemorrhagic emergencies unamenable to surgical haemostasis.

References