Usefulness and risk of erythropoietin therapy in pregnancies with chronic renal insufficiency

Sir,

Data regarding usage of recombinant human erythropoietin (rHuEPO) in pregnancy are limited, and they are mostly restricted to pregnancy of women on regular dialysis. Few experiences exist about the risk and benefit of rHuEPO in pregnancies of patients with renal insufficiency not requiring dialysis. To our knowledge only seven cases (including three transplant patients) have been reported [1-3]. The rHuEPO treatment can lead to the development or worsening of hypertension in about 1/3 of patients, but in predialytic situations it has no effect on the progression of renal failure. Pregnant women with renal insufficiency are already at high risk for preeclampsia and progression of renal failure. The effect of erythropoietin on these complications is questionable. We report the results of rHuEPO therapy in two pregnant women with severe anaemia of chronic renal failure.

Case 1. A 23-year-old primigravida was admitted to the obstetric clinic at 19 weeks’ gestation with chronic renal insufficiency. Agenesia of the right kidney was revealed 1 year before and percutaneous angioplasty was performed for stenosis of left renal artery at the time. After intervention her blood pressure normalized and renal function remained stable. At her first nephrological visit blood pressure was 110/70 mmHg, serum creatinine was 194 μmol/l and Htc was 0.28. Urine analysis revealed 0.54 g/l proteinuria, pyuria, and significant bacteriuria. We initiated amoxicillin treatment, with folic acid and iron supplementation. Urinary tract infection was cured but anaemia worsened and Htc decreased gradually to 0.23 at 25 weeks’ gestation. Subcutaneous rHuEPO at a dose of 2000 U (38 U/kg) was started three times a week. Temporarily oral iron supplementation was switched to intravenous form. The dosage of rHuEPO was increased to 4000 U three times a week at 28 weeks’ gestation because of the slow increase in Htc. Two weeks later the Htc increased to 0.33 and the dosage of rHuEPO was decreased to 2000 U once a week. This dosage was maintained throughout the rest of pregnancy. The Htc and serum creatinine remained stable and blood pressure did not change. The rest of pregnancy was uneventful. The patient delivered a 2100 g male infant with 5-min Apgar score of 10 at 39 weeks’ gestation. At delivery her Htc was 0.35 and serum creatinine was 205 μmol/l. No postpartum and neonatal problems occurred.

Case 2. A 21-year-old primigravida registered for prenatal care at 13 weeks’ gestation. She had no problems in her history, but the urine analysis revealed pyuria and proteinuria. After treatment with ampicillin pyuria relapsed and chronic renal insufficiency was revealed. She was hospitalized and referred to nephrological visit at 18 weeks’ gestation. She was free from complaints and her blood pressure was 110/70 mmHg. The 24-hour urine collection contained 2.0 g protein and 15-20 leukocytes and 2–3 red blood cells per high power field were seen in the urinary sediment. The serum creatinine was 317 μmol/l, Htc was 0.26. Cefuroxim axetil was started with oral iron and folic acid supplementation. Pyuria disappeared and serum creatinine decreased slightly but Htc declined to 0.24 at 20 weeks’ gestation. Subcutaneous rHuEPO was started at dose of 2000 U (42 U/kg) three times a week with concomitant intravenous iron. Six weeks after initiation of rHuEPO therapy the Htc increased to 0.34 and the dosage of rHuEPO was decreased to 2000 U two times weekly. At 29 weeks’ gestation hypertension and oedema developed. Methyldopa and nifedipine were started and rHuEPO was discontinued because of the high Htc of 0.37. Worsening preeclampsia necessitated induction of labor at 31 weeks’ gestation. At that time her serum creatinine was 338 μmol/l and Htc was 0.36. Cesarean section resulted in delivery of 1280 g infant with 5-min Apgar scores of 8. After delivery blood pressure and volume status normalized gradually, but the serum creatinine increased. The patient was discharged with a serum creatinine of 468 μmol/l on postoperative day 14. Five months later her serum creatinine and Htc were 480 μmol/l and 0.34 respectively.

Pregnancy increases the demand for erythropoietin, e.g. in pregnant uraemic patients an increased dose of rHuEPO is required to maintain Htc [4,5]. We did not measure the serum erythropoietin, but we believe that the anaemia was caused by maternal anaemia. No adverse effects of rHuEPO were noted in the infants, their postpartum haemoglobin and thrombocyte values were normal.

In Case 2 no side effects of rHuEPO therapy was observed and the renal function remained stable. While in Case 2
hypertension appeared after 9 weeks of rHuEPO therapy, leading to termination of pregnancy 2 weeks later. Her renal function worsened significantly. It is difficult to differentiate between preeclampsia and hypertension caused by rHuEPO therapy. Four of the previously reported seven patients [1–3] had worsening renal function during pregnancy. Severe preeclampsia appeared in three of the seven cases and was believed due to superimposed preeclampsia. In our case we couldn't exclude the contributory role of rHuEPO therapy because the occurrence of hypertension was associated with elevation of Htc of 0.37. Our experiences would lend support to the use of rHuEPO in pregnancies complicated by severe anaemia of renal failure, but only partial correction of anaemia and careful monitoring by experienced nephrologist and gynaecologist are required to diminish the risk of hypertension and progression of renal failure.

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Azathioprine-induced hepatic veno-occlusive disease in a renal transplant recipient: histological regression following azathioprine withdrawal
Sir,

Hepatic veno-occlusive disease (VOD) has been described in renal transplant recipients on azathioprine, although a cause-and-effect relationship in this situation has not yet been well established. We report a patient with azathioprine-induced VOD who showed regression of histological lesion after withdrawal of the drug.

A fifty-year-old male received a live renal allograft from his brother in January 1990. He received triple drug immunosuppression comprising cyclosporin, azathioprine, and prednisolone for the first year, after which cyclosporin was stopped and the azathioprine dose was increased from 1 mg/kg to 2 mg/kg. In January 1993 he presented with generalized weakness, fever, and weight loss of around 3 kg, of 3 weeks duration. On examination there was moderate pallor but no lymphadenopathy, jaundice, or oedema. The liver was palpable 4 cm below the costal margin and liver span was 13 cm. There were no signs of portal hypertension.

Investigations revealed Hb of 85 g/l, normal total and differential leukocyte counts, erythrocyte sedimentation rate 30 mm/h, serum creatinine of 106 μmol/l, serum bilirubin 34.2 μmol/l, with conjugated fraction 22.1 μmol/l. Aminotransferases were normal, serum alkaline phosphatase was 3.8 μkat/l while serum proteins were 67 g/l with albumin 34 g/l. HBsAg was negative. Ultrasonography of liver showed focal hypechoic areas, while the spleen and allograft were normal. Upper gastrointestinal endoscopy was normal. Liver biopsy showed normal lobular architecture. The portal tracts showed mild fibrosis and a mixed inflammatory cell infiltrate. In addition there was marked centrizonal sinusoidal dilatation and haemorrhagic necrosis (Figure 1). The hepatic cords in the centrizonal area were thinned out and atrophic. The central vein outline could not be seen in some of the centrizonal haemorrhagic areas, but in occasional lobules the central vein lumen with subintimal oedema. The reticulin stain showed fibrosis around the central vein in these areas. There was reticulin collapse and condensation in the centrizonal area (Figure 2). These features were suggestive of VOD. There was also focal hepatocyte necrosis and occasional acidophil-like bodies. Orcein stain was negative. Serial sections studied did not show any evidence of granulomatous inflammation.

The patient also developed azathioprine-induced bone marrow depression. Azathioprine was therefore stopped and

Fig. 1. Photomicrograph of liver showing a central vein with occlusion of its lumen and surrounding haemorrhage. The centrizonal sinusoids show dilatation and congestion (H&E, ×280).

Fig. 2. Reticulin-stained preparation of liver biopsy. Centrizonal areas reveal laying down of thick reticulin fibres along with dilated sinusoids (Reticulin stain, ×280).

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