ERYTHROPOIETIN USE IN PREGNANCY: TWO CASES AND A REVIEW OF THE LITERATURE

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ABSTRACT

End-stage renal disease complicates only a small percentage of pregnancies, but, of these, virtually all become anemic due to a deficiency in erythropoietin. Erythropoietin has been shown to correct anemia due to renal disease in nonpregnant patients. We report two cases of erythropoietin use during pregnancy complicated by severe anemia due to renal failure. No maternal or fetal side effects were noted. Our two cases exemplify that erythropoietin is an effective means of treating anemia due to renal disease in the gravid patient.

Keywords: Erythropoietin; anemia; renal failure; pregnancy

End-stage renal disease is a rare complication of pregnancy. When it does occur, virtually 100% become severely anemic due to a deficiency in erythropoietin.[1,2] Moreover, platelet function in these patients is often poor.[3] This presents a therapeutic dilemma for the gravid patient with renal failure, as vaginal delivery or cesarean section in the presence of chronic anemia and abnormal platelet function can result in excessive blood loss and the need for multiple transfusions.

Erythropoietin is available via recombinant DNA technology (rHuEpo) and has been shown to be efficacious in reversing the anemia associated with chronic renal failure in the nongravid patient.[2,4,5] We describe two cases of recombinant human erythropoietin use in pregnancy complicated by anemia due to chronic renal insufficiency.

CASE REPORTS

Case 1

A 22-year-old white primigravida with chronic hypertension and a recent cadaveric renal transplant presented at 8 weeks' gestation. Her past medical history was significant for end-stage renal disease due to chronic reflux requiring transplantation and subsequently an infected lymphocele, which caused worsened renal function. She was maintained on prednisone, cyclosporine, hydralazine, clonidine, and furosemide. At 32 weeks' gestation, she was admitted for another infected lymphocele, which was percutaneously drained. Laboratory analysis revealed a hematocrit of 19.9%, potassium of 5.2 mEq/L, blood urea nitrogen of 32 mg/dL, creatinine of 2.5 mg/dL, erythropoietin of 137 mU/mL (normal 17 to 50 mU/mL), and normal iron studies. The peripheral smear was consistent with a normochromic, normocytic anemia. She was treated with 143 U/kg (10,000 U) rHuEpo (Epogen; Amgen, Newbury Park, CA) subcutaneously three times a week, which was continued on an outpatient basis. Her hematocrit and reticulocyte count 16 days after starting rHuEpo were 28% and 5.2%, respectively. Her blood pressure remained unchanged from baseline during treatment (120–150/70–90 mm Hg). The rHuEpo was discontinued at 36 weeks' gestation when her hematocrit was 33%. She was admitted at 38 weeks' gestation for oxytocin induction of labor and spontaneously delivered a healthy 3160 g female. No adverse neonatal effects were noted.

Case 2

A 20-year-old black primigravida with chronic hypertension presented for prenatal care at 23 weeks' gestation with pitting edema, 4+ proteinuria, and a blood pressure of 150/100 mm Hg. She was admitted to the hospital for further evaluation. The nifedipine and indapamide she had been maintained on were discontinued and she was treated with labetalol 100 mg orally twice a day. Blood pressures on bed rest declined to 140/80 mm Hg. A 24-hour urine collection showed 7452 mg of protein and a creatinine clearance of 43 mL/min. Additional laboratory values included a serum creatinine of 2.9 mg/dL, blood urea nitrogen of 33 mg/dL, hematocrit of 23%, platelets of 295,000, potassium of 4.4 mEq/L, and negative antinuclear antibody. A renal sonogram demonstrated normal-sized kidneys without hydronephrosis, but increased echogenicity consistent with renal parenchymal disease. Her blood pressure increased gradually, necessitating increases

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in her labetalol dosage to a maximum of 1800 mg/day to maintain blood pressures of 140–150/90–98 mm Hg. Her renal function progressively worsened, as did her anemia (creatinine clearance of 28 mL/min and hematocrit of 17.8%). A regimen of 45 U/kg (4500 U) rHuEpo subcutaneously three times a week was initiated. The erythropoietin level before treatment was 32 mU/mL. A renal biopsy showed advanced focal and segmental glomerulosclerosis involving at least 50% of the glomeruli. One week after starting rHuEpo, her reticulocyte count was 5.1% and her erythropoietin level was 65 mU/mL. At 28 weeks' gestation (10 days after beginning rHuEpo), she developed asymptomatic, superimposed severe preeclampsia, with diastolic blood pressures of 120 mm Hg, requiring cesarean delivery. Laboratory analysis revealed a hematocrit of 19.7% (an increase of 2%), platelets of 288,000, reticulocyte count of 6.8%, and creatinine of 4.1 mg/dL. After receiving 100 cc of normal saline, the patient received 1 U of packed red blood cells over 15 minutes. Just prior to induction of general anesthesia, about 45 minutes after the transfusion, her blood pressure was 180/140 mm Hg. This was controlled with 30 mg intravenous labetalol. A healthy 1080 g female infant was delivered. Postoperatively, she received the same regimen of labetalol and rHuEpo. Within 48 hours, she was normotensive. Her 24-hour postoperative hematocrit was 22%. On postoperative day 8, she had a hematocrit of 19.7%, reticulocyte count of 3.2%, creatinine of 3.6 mg/dL, and erythropoietin level less than 19 mU/mL. She was discharged home on an increased dose of rHuEpo, 6000 U three times weekly. No adverse neonatal effects were noted.

DISCUSSION

Erythropoietin is a glycoprotein hormone, produced by the kidney, that increases red blood cell mass in response to stimulation of bone marrow production of red blood cell progenitors.[6] Erythropoietin is available via recombinant DNA technology and has been effective (90% success rate) in reversing the anemia associated with end-stage renal disease in nonpregnant patients.[2,4,5]

Erythropoietin levels vary widely in pregnancy, as in the nonpregnant state. Mean erythropoietin levels at 8 to 10 weeks' gestation range from 8 to 18 mU/mL and increase gradually, peaking during the third trimester (17 to 50 mU/mL) and then decreasing slightly by 40 weeks' gestation (11 to 90 mU/mL).[6–9] Erythropoietin remains elevated in the immediate postpartum period.[7] Although some reports have supported a correlation between human placental lactogen and erythropoietin[8] others studies have not.[7]

Recommended dosage regimens of rHuEpo are generally based on the patient's weight (25 to 150 U/kg) and titrated according to response and the target hemoglobin. Administration is either subcutaneous or intravenous injections two to three times per week.[2,5,10,11] Candidates for rHuEpo treatment must have adequate iron stores, an absence of cardiovascular complications (such as uncontrolled hypertension), an erythropoietin-deficient anemia, and require regular blood transfusions to maintain a hematocrit greater than 30% or have a hematocrit that is persistently less than 20%.[11] The first evidence of a peripheral response is an increase in reticulocyte count within 2 to 5 days of starting therapy.[7] Subsequently, an increase in hematocrit should be apparent within the next 2 weeks, averaging about 2 to 3% per week.[5] Individual responses vary widely and the dose should be titrated as necessary every 2 to 3 weeks.[5,11]

Treatment with rHuEpo may be associated with side effects. Patients who receive an intravenous bolus will often experience a flulike syndrome, usually beginning 1½ to 2 hours after the injection, with spontaneous resolution within 10 to 12 hours.[2] Some patients experience asymptomatic conjunctival inflammation, which requires no treatment.[2] A small percentage of patients may experience seizures.[5,11] In some patients there appears to be a tendency toward thrombotic events, which may be due to the increased fibrinogen levels and improved platelet function seen with erythropoietin use.[2,3,5]

Perhaps the most significant side effect is the development or worsening of hypertension.[3,5,10,11] This is of particular concern in the gravid patient with renal disease because she is already at risk for the development of preeclampsia and intrauterine growth retardation. The etiology of the elevation in blood pressure is unclear, although it is unlikely that erythropoietin has a direct pressor effect.[11] The development of hypertension parallels the increase in hematocrit, occurring when the hematocrit increases rapidly or when it becomes greater than 30 to 35%. It may be related to an increase in red blood cell viscosity or a loss of chronic hypoxic vasodilation because a blood transfusion given to a patient who is chronically anemic may also cause a rapid increase in blood pressure,[5,11] as we saw with our second patient.

Fortunately, the hypertension associated with erythropoietin use can be controlled with antihypertensive medications or by allowing the hematocrit to decrease slightly if it is more than 32 to 35%.[2,5,11] In general, it is recommended that the anemia be corrected gradually (2 to 3% rise per week) and to maintain the hematocrit between 30 and 35% to avoid a significant increase in blood pressure.[2,10,11]

Both of our patients responded well to therapeutic doses of erythropoietin. The first patient had a significant increase in hematocrit and did not develop worsening hypertension. The second patient did not receive treatment long enough to see a large increase in hematocrit, but she had an elevated reticulocyte count consistent with a marrow response to erythropoietin as well as a 2% rise in hematocrit 10 days after beginning therapy. The decreases in the reticulocyte count and erythropoietin level after delivery were probably due to a transfusion-induced bone marrow suppression. The obvious question is whether her worsening hypertension was due to erythropoietin or to superimposed preeclampsia. We believe that it was superimposed preeclampsia for two reasons. Hypertension associated with erythropoietin treatment is linked to an increase in hemoglobin and hematocrit (generally greater than 10 mg/dL and 30%, respectively); she had not yet had a significant increase in red blood cell mass when her blood pressure worsened. After delivery, she was maintained on her predelivery dose of labetalol and continued the same regimen of erythropoietin. She became normotensive within 48 hours after delivery, a finding consistent with preeclampsia.

McGregor et al[12] and Yankowitz et al[13] have recently reported on a total of four gravid patients with renal disease who had favorable results with erythropoietin therapy. Hou et al[14] described five additional women who were on dialysis during their pregnancies. Three of these women required erythropoietin prior to conception to avoid transfusions. Only two of the five patients maintained or increased their hematocrit levels during pregnancy. The others were iron deficient and all were on relatively low doses of erythropoietin (2000 to 4000 U three times a week). Of note, only one woman, a patient

with lupus who had a history of nephrotic range proteinuria and severe hypertension in a previous pregnancy, had difficulties with blood pressure control. She became hypertensive at 26 weeks' gestation and subsequently delivered a stillborn, 350 g fetus at 27 weeks' gestation. The increase in her blood pressure was more likely a manifestation of her disease rather than a side effect from the erythropoietin therapy.

The benefit of erythropoietin therapy is that it potentially provides a means to reverse anemia in the pregnant patient with renal disease without having to resort to blood transfusions. If the rise in hematocrit is controlled and maintained around 32%, the likelihood of hypertension is minimized. Although the risks of hypertension, seizures, and thrombosis cannot be ignored, it seems that erythropoietin therapy may be a viable alternative to long-term anemia or recurrent transfusions and is not likely to cause significant adverse effects in the gravid patient with renal failure.

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