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When blood is not an option: Optimal bloodless management of severe anemia in pregnancy

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Abstract

Standard treatment for severe anemia in pregnancy is allogeneic blood transfusion, but this is not acceptable to all patients. Options for alternative anemia treatment are available. In this case report, a 32-year-old G2P1 woman who was a Jehovah's Witness presented at 27 weeks gestation with dyspnea, palpitations, and severe anemia (hemoglobin 2.8 g/dL) related to chronic rectal bleeding. She declined blood transfusion. An anemia management protocol (high-dose erythropoietin-stimulating agent, iron, vitamin D, vitamin C, folate, vitamin B12) rapidly increased endogenous erythropoiesis. After 12 days, hemoglobin increased to 8 g/dL. A bovine hemoglobin-based oxygen carrier was available for acute bleeding but was not used. This case highlights that early initiation of multimodal therapy can adequately increase endogenous erythropoiesis to treat life-threatening anemia in antepartum patients who do not accept blood transfusion.

Key words: anemia, bloodless medical and surgical procedures, erythropoiesis, hemoglobin, pregnancy.

Introduction

Management of pregnant patients with severe life-threatening anemia most commonly includes allogeneic blood transfusion. In patients who do not accept transfusion on religious grounds or for other reasons, providing effective, timely treatment is critical. It is therefore imperative to have alternative treatment options readily available. Alternative treatment should focus on increasing endogenous erythropoiesis, controlling hemorrhage, and utilizing hemoglobin-based oxygen carriers.

An abundance of literature exists on strategies to manage blood loss in patients with anemia who opt out of allogenic transfusion in the peri- and postpartum periods. However, there is limited evidence on effective, safe regimens for treatment of severe anemia in the antepartum period. This case report therefore details a multimodal regimen utilized at 27 weeks gestation that effectively increased maternal hemoglobin without allogenic blood transfusion and ultimately resulted in a term delivery.

Case

A 32-year-old G2P1 woman at 27 weeks gestation who was a Jehovah's Witness and had a past medical history of pre-eclampsia with severe features presented to her obstetrician with 2 weeks of shortness of breath and palpitations. She also reported acute on chronic rectal bleeding. Upon transfer to the emergency department, she was found to have a hemoglobin of 2.8 g/dL. She was counseled by the referring hospital providers about the risk of maternal and fetal death with severe anemia, and ultimately declined allogeneic blood transfusion for religious reasons. She was transferred to our intensive care unit for initiation of a treatment protocol for severely anemic patients who do not accept allogeneic blood transfusion.

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Upon arrival, we confirmed her wishes regarding all blood components and derivatives.[1] We immediately initiated our protocol for multimodal treatment of severe anemia (Figure 1), which included three key components: (1) augmenting endogenous erythropoiesis, (2) controlling hemorrhage, and (3) utilizing hemoglobin-based oxygen carriers when indicated.[2] To augment and support endogenous erythropoiesis,

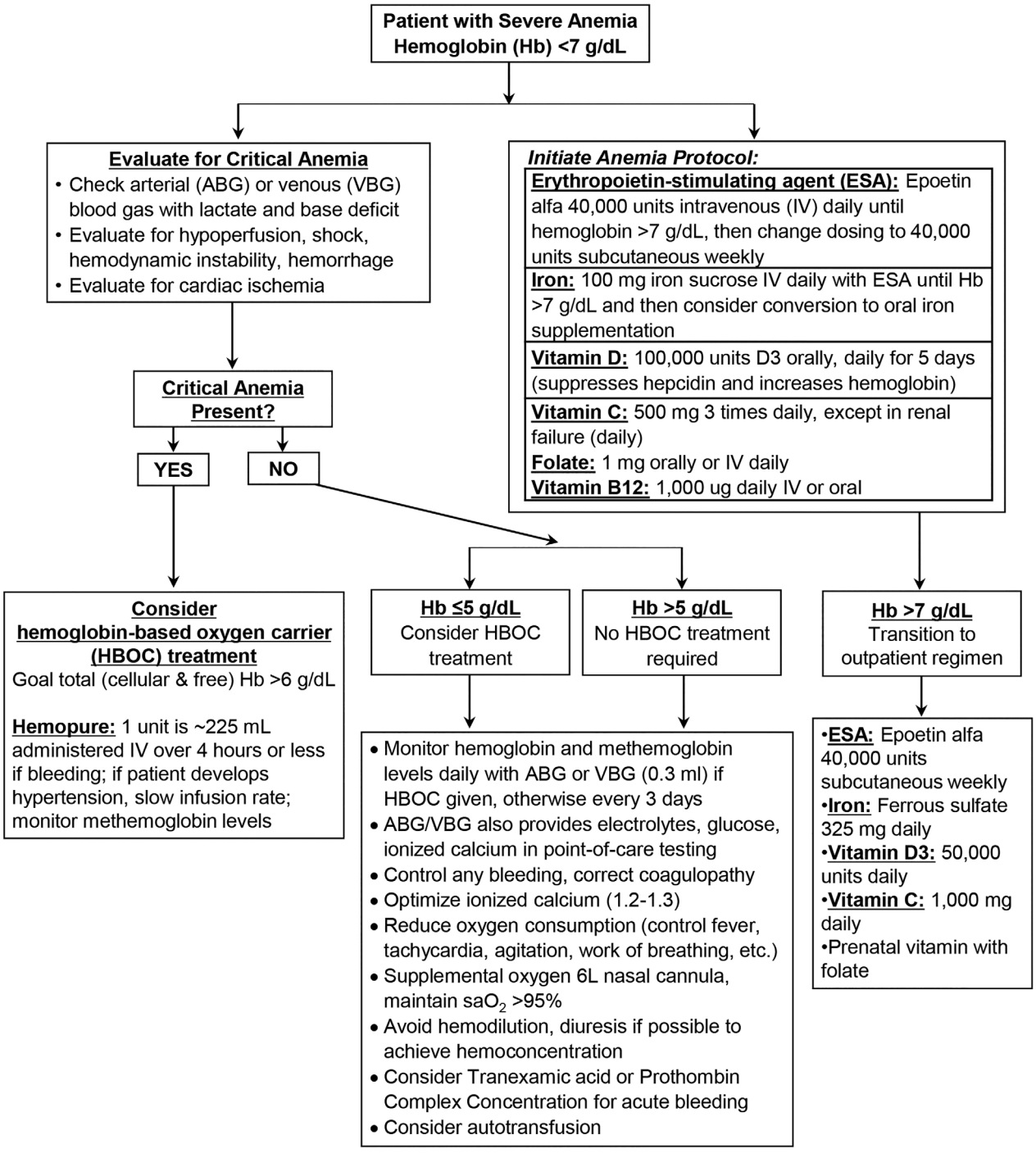

Figure 1 Modified severe anemia bloodless treatment protocol: when blood is not an option

she was started on daily erythropoietin-stimulating agent and intravenous iron sucrose. Vitamin D3 was given to suppress hepcidin and increase hemoglobin. Additional vitamins and co-factors, including vitamin C, folate, and vitamin B12, were also administered. Venous blood gas was obtained every 3 days to monitor hemoglobin, lactate, and base deficit (Figure 2). Other blood draws were avoided to minimize blood loss. When her hemoglobin rose above 7 g/dL, erythropoietin-stimulating agent dosing was spaced from daily to weekly and iron and vitamin supplementation was transitioned from intravenous to oral. Additional supportive care was also provided, including bedrest with supplemental oxygen (6 L nasal cannula) to achieve oxygen saturations >95% to support fetal oxygenation, telemetry, and frequent blood pressure and pulse oximetry monitoring. Intravenous fluids were minimized. Given that she received a significant amount of crystalloid prior to transfer and hemodilution was suspected, furosemide 10 mg IV daily was administered until her hemoglobin rose above 7 g/dL. Her fluid balance remained net negative.

To control hemorrhage from her gastrointestinal bleeding, we initiated empiric treatment with pantoprazole 80 mg IV twice daily and tranexamic acid (1 g IV bolus, 3 g infusion over 24 h). Physical examination confirmed external hemorrhoids. Because of the severity of anemia, she could not safely undergo further diagnostic or therapeutic interventions to determine the etiology of her bleeding. A bowel regimen for treatment of constipation was started (docusate 100 mg by mouth twice daily and polyethylene glycol by mouth daily). Lower gastrointestinal bleeding ceased with these measures.

We discussed utilizing Hemopure (Hemoglobin Oxygen Therapeutics LLC, Souderton, PA), a bovine hemoglobin-based oxygen carrier (HBOC-201), with the patient on admission and reviewed all potential benefits and risks. Hemopure consists of purified, glutaraldehyde-polymerized bovine hemoglobin; it is not approved by the US Food and Drug Administration (FDA) for any indication in humans but is available through clinical trials or by the FDA's Expanded Access Program for the treatment of patients with

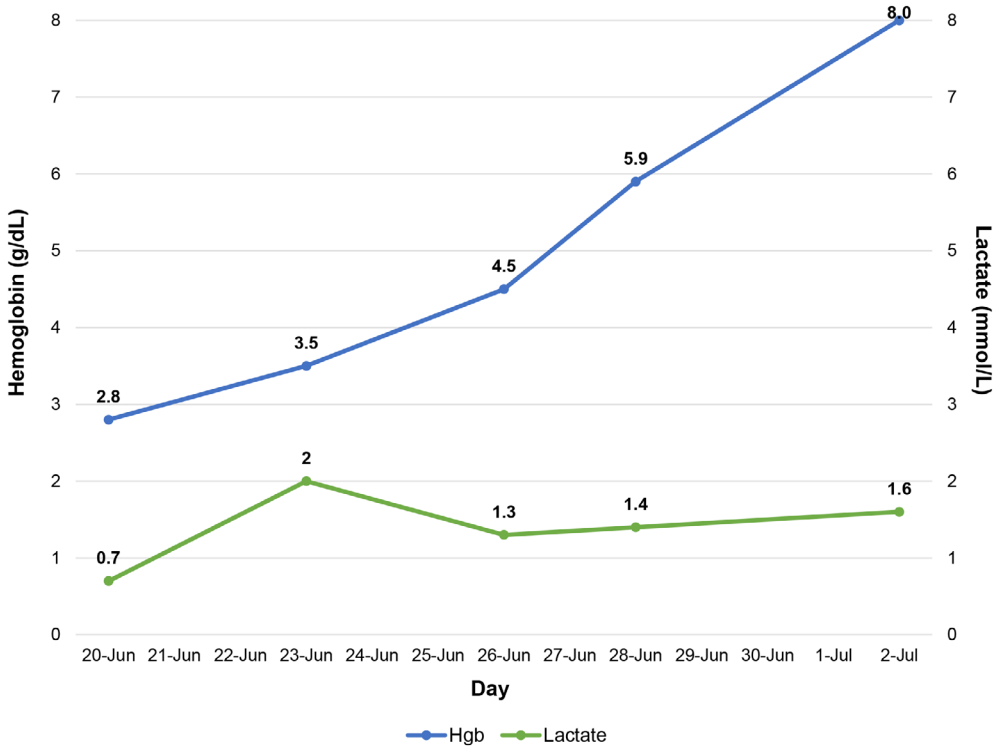

Figure 2 Changes in hemoglobin and lactate over time with severe anemia bloodless treatment protocol. Time-dependent changes in hemoglobin (g/dL) and lactate (mmol/L) after initiation of severe anemia bloodless treatment protocol on hospital admission

severe, life-threatening anemia for whom allogeneic blood transfusion is not an option. The patient signed consent for Hemopure if required for acute hemorrhage. Given that bleeding stopped prior to discharge, Hemopure was not required during her admission.

From an obstetric standpoint, ultrasound demonstrated severe fetal growth restriction (second percentile) with normal umbilical artery Dopplers. This was attributed to her profound acute on chronic anemia. Fetal anatomy and amniotic fluid volume were normal. Fetal heart tones were monitored daily with bedside Doppler. Nonstress testing was not initiated, as the patient was not a candidate for cesarean delivery should fetal distress be detected due to the severity of anemia. Evaluation was also notable for gestational hypertension.

The anemia management protocol (high-dose erythropoietin-stimulating agent, iron, vitamin D, vitamin C, folate, vitamin B12) was successful in increasing endogenous erythropoiesis, which was confirmed by an elevated reticulocyte count. After 12 days, hemoglobin increased from 2.8 to 8 g/dL (Figure 2). She was discharged home on daily oral ferrous sulfate, vitamin C, vitamin D3, a prenatal vitamin, and a bowel regimen. Outpatient antenatal testing and a referral to gastroenterology were arranged.

Gastroenterology evaluation confirmed external hemorrhoids, which were the presumed source of bleeding. Magnesium oxide 400 mg twice daily was added to her bowel regimen. Postpartum colonoscopy was recommended to evaluate for alternative causes of rectal bleeding.

The patient's hemoglobin increased from 8 g/dL at discharge to 10.1 g/dL at 31 weeks gestation. Due to incomplete adherence to the regimen of iron, vitamins, and stool softeners, rectal bleeding increased; hemoglobin subsequently decreased to 6.7 g/dL at 34 weeks gestation. After resumption of the outpatient regimen, hemoglobin increased to 10.2 g/dL at 36 weeks gestation. At this time, fetal growth restriction persisted at the fourth percentile. Umbilical artery Dopplers remained normal and antenatal testing was reassuring.

The patient underwent scheduled repeat cesarean delivery at 37 weeks gestation with gestational hypertension, fetal growth restriction, and history of prior cesarean as indications. A live female infant was delivered weighing 2140 g with Apgar scores of 8 and 9 at 1 and 5 min, respectively. Surgery was uncomplicated, with a quantitative blood loss of 400 mL. Pre-operative hemoglobin was 10.7 g/dL and postoperative day 1 hemoglobin was 8.8 g/dL. The patient and neonate were discharged in good condition on postpartum day 2. Hemoglobin at the patient's routine postpartum visit was 10.9 g/dL.

Discussion

Management of pregnant patients with severe anemia who do not accept blood transfusion in the antepartum period can present significant clinical and ethical challenges. Competent pregnant adults have the right to decline blood transfusion, but it is imperative to ensure that the patient has decision-making capacity, that their refusal of that specific treatment is appropriately informed, and that they understand the potential risks and consequences of refusal.[3] Once this is confirmed, physicians must respect patient autonomy and the patient's right to decline specific treatments. Clinicians should be careful not to interpret that patient refusal of allogeneic blood transfusion indicates that all other recommended medical care will also be declined. Alternative anemia treatment strategies should be discussed with the patient. It is important for all practitioners to have knowledge about options to augment endogenous erythropoiesis, minimize blood loss, and utilize methods to improve physiologic response to severe anemia. Detailed discussion about potential bloodless options can reduce maternal and fetal mortality associated with severe anemia.

There is a paucity of studies on antepartum management of severe anemia and obstetric outcomes in the Jehovah's Witness population. A retrospective review of all cases of maternal mortality and serious maternal morbidity in the Netherlands over more than 20 years showed a six times increased risk for death in Jehovah's Witness patients (primarily due to obstetric hemorrhage) and a more than three times increased risk for serious maternal morbidity compared to the general population.[4] A review of studies in nonpregnant patients also confirms high mortality associated with severe anemia. A study of 293 Jehovah's Witness patients who declined blood transfusion reported an 8.2% mortality rate. There was a twofold increase in mortality risk per each 1 g/dL decrease in nadir hemoglobin (unadjusted odds ratio [OR] 1.04, 95% confidence interval [CI] 1.52–2.74; adjusted OR 1.82, 95% CI 1.27–2.59). Similarly, mortality was highest (>50%) in patients with hemoglobin ≤3 g/dL.[5] These studies confirm the high morbidity and mortality associated with severe life-threatening anemia in patients who decline blood transfusion.

Our evidence-based protocol for treatment of severe anemia is highly effective and safe in the antepartum period. We have recently added Vitamin D3 to our protocol to rapidly augment endogenous erythropoiesis and increase hemoglobin.[5–7] In patients with acute bleeding or signs of critical anemia, all measures to support cessation of hemorrhage must be initiated. Correction of any associated coagulopathy in bleeding patients is essential; tranexamic acid or prothrombin complex concentrate can be considered.

Though hemoglobin-based oxygen carrier treatment with Hemopure was not required in this case, we discussed it fully with the patient in preparation for use in acute hemorrhage if required. It is best to have a detailed discussion of hemoglobin-based oxygen carrier potential risks and benefits when the patient is stable rather than in the emergent situation. In 2001, Hemopure was approved in South Africa for the treatment of adult surgical patients who are acutely anemic for the purpose of eliminating, delaying, or reducing the need for allogeneic red blood cell transfusions. In 2010, Hemopure was also approved in the Russian Federation for the treatment of acute, all-cause anemia. A planned clinical study sponsored by the US Department of Defense will evaluate the use of Hemopure for treating trauma patients with hemorrhagic shock in the pre-hospital setting in South Africa (n = 1400 over 3 years). Hemoglobin-based oxygen carriers have been successfully used in peripartum hemorrhage.[8] Additionally, sedation and ventilator support have been reported as an alternative strategy to decrease oxygen consumption in the case of severe anemia in a critically ill patient who declines blood transfusion.[9] Though this option was not pursued in this case, it could be considered in similar clinical scenarios.

Although severe life-threatening anemia is more common in the peri- and postpartum periods related to uterine bleeding, rather than in the antenatal period as in this case, the management principles are similar.[10–13] Early initiation of an aggressive anemia treatment protocol can quickly increase endogenous hemoglobin and improve maternal and fetal outcomes.

Conflict of interest

The authors declare no conflicts of interest for this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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