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Efficacy and safety of adjuvant recombinant human erythropoietin and ferrous sulfate as treatment for iron deficiency anemia during the third trimester of pregnancy

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ABSTRACT

Purpose: Gestational anemia increases the incidence of maternal and fetal complications. Adjuvant recombinant human erythropoietin (rHuEPO) has been used in patients who refuse blood transfusions, have a low response to treatment with iron sulfate, have limited time before birth, or have other illnesses that complicate the anemia. We demonstrated that the use of adjuvant rHuEPO with iron sulfate reduces the anemia time period and is innocuous to the fetus.

Method: An experimental longitudinal prospective study; 100 pregnant women in their third trimester were included. Group 1 ($n = 50$) was set as control for prevalence of anemia and establish hematological maternal and fetal parameters at delivery for our population; 50 women diagnosed with iron deficiency anemia were randomly assigned to treatment groups. Group 2 ($n = 25$) third trimester women with a hemoglobin of <11 g/dL were treated with iron sulfate, 600 mg administered orally daily for 4 weeks, evaluating the hematologic response for the mother weekly and for both mother and fetus at birth; Group 3 ($n = 25$) women similar to group 2, treated in addition with adjuvant rHuEPO, 4000 units subcutaneously, three times a week, for 4 weeks evaluating the same parameters.

Results: Group 2 and 3 showed a corrected anemia before delivery (mean 11.1 vs 11.4 g/dL), but Group 3 showed a statistically broader and more rapid increase in hemoglobin (1.22 vs 1.92 g/dL, p value 0.013) with an rHuEPO dose of 4000 units, three times a week for 1 month. No clinical or hematologic difference or changes in growth were observed in the fetus.

Conclusions: Erythropoietin is safe and effective for both mother and fetus, although an ideal pregnancy dose has not yet been established.

Introduction

During pregnancy there is a significant increase in the amount of iron required due to elevated erythrocyte cell mass, plasma volume expansion, and development of the fetus–placenta complex [1]. This elevates the risk of gestational anemia in pregnant women without vitamin supplements. The World Health Organization evidenced a direct correlation between socioeconomic status and gestational anemia, showing a prevalence of 52% in non-developed or developing countries, against 20% in industrialized countries. The highest prevalence was found in India (88%), followed by Africa (50%), Latin America (40%) and the Caribbean (30%) estimating a global average of up to 42% [2,3].

The National Health and Nutrition Examination Survey (ENSANUT) 2012 (Mexico) reported a prevalence of gestational anemia of 17.9% in Mexican population (12–49 years of age) with the highest

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prevalence in age groups of 12–19 years (19.6%) and 30–39 (19.0%). Only 11.6% of women without pregnancy exhibit anemia [4].

The etiology of gestational anemia may include the most common causes: deficiencies of iron, folate, vitamin B-12, vitamin A, amongst others [5]. These may be due to inadequate diets of insufficient supplements [6], and may be present by themselves or in combination with other pathologies such as thalassemias. Sanchaisuriya et al. reported a 25.4% thalassemia relation to iron deficiency in pregnant women in northeast Thailand [7]. Other studies have reported a thalassemias incidence of 7.3% of in women [8]. However, the diagnosis of these may be complex and difficult to diagnose in public health institutions [5]. Many times, bone marrow aspirate, peripheral blood smear and genetic disorder tests are needed to identify the more rare causes of anemia [9], presenting a challenge in pregnant women due to the cost and invasive nature of the procedure.

The majority of gestational anemia cases (95%) are caused by iron deficiency [10]. The WHO describes it as a reduction of the metabolic iron reserves causing clinical manifestations. The diagnosis is established by blood tests showing decreased serum ferritin and hemoglobin (Hgb) levels [11]. However, iron deficiency anemia may be diagnosed with a complete blood count (CBC) based on the mean volume (<60 fL), volume dispersion and mean hemoglobin concentration (<280 g/L) [12,13]. When ferritin levels are not available, a microcytic hypochromic anemia is suggestive of iron deficiency (sensitivity of 94% and specificity of 92.3%) and helps differentiate from other causes of anemia [12,13]. Gestational anemia is established by the Hgb levels according to the stage of pregnancy, using as reference 11 g/dL in the first trimester, <10.5 g/dL in the second, and <11 g/dL in the third [14].

Approximate 1190 mg of iron is needed from conception to delivery to maintain a healthy pregnancy [15]. The daily requirements are 4–5 mg, which cannot be obtained only with the physiological increase of intestinal absorption even with an optimal diet. The net balance of iron during pregnancy, childbirth and postpartum is a deficit of 580 mg. This means, the iron balance is inevitably negative in each pregnancy, manifested through a low serum ferritin concentration [16].

Gestational anemia raises the risk for several complications for bother mother and fetus. These include premature birth, low birth weight, intrauterine growth restriction, stillbirth, premature rupture of membranes and increased susceptibility to infection [16]. Placental development is also affected by anemia and hypoxia, causing abnormal trophoblast invasion and release hypoxia inducible factor. This consequently increases the incidence of placenta previa and preterm placenta abruption [10,17–20]. Mireku et al. report a link between mothers who had anemia lower than 9 g/dL during pregnancy with a lower cognitive and motor development in one-year-old children [21].

There is a select group of gestational women who have a higher risk of morbidity and maternal/fetal mortality. These include patients who refuse blood transfusions, who have rare blood types, intolerance or lack of response to oral therapy, limited time due to late gestation, or comorbidities that complicate the anemia (renal failure, gastrectomy, among others) [22]. This necessitates the use of effective and expeditious strategies for the correction and treatment of gestational anemia. The use of rHuEPO has been a viable option to this problem [23].

Erythropoietin is a glycosylated polypeptide of 166 amino acids with molecular weight of 34–39 kDa. It has a serum half life of 4–13 h, is produced in the peritubular interstitial cells and kidney mesangial cells in response to tissue hypoxia and anemia. It promotes erythroid progenitors to maintain cell viability and proliferative stimulus of erythroid, and achieve the desired level of hematocrit. Healthy individuals maintain a mean concentration of 10–20 U/L, which is enough to boost daily production of red blood cells. Anemia patients treated with rHuEPO show increased concentration of about 100–500 U/L [24].

The rHuEPO can be produced using recombinant DNA technology. It has proven to be effective as an adjunct to ferrous sulfate in the treatment of gestational anemia, as it is safe for the mother and fetus, and it does not cross the placental barrier [23–26]. The effect lasts up to 2 weeks administration is stopped [27].

The aim of our study was to demonstrate the safety and efficacy of rHuEPO in gestational anemic patients. The purpose was to evidence that a low dose can improve the anemia in the mother without modifying fetal hematologic variables.

Patients and methods

Inclusion criteria. Pregnant women in their third trimester between 31 to 35.5 weeks of gestation (WOG) who had not received previous anti-anemic treatment.

Exclusion criteria. Patients with hypertension (gestational or non-gestational), organic or hematologic disorders, pregnancy above 35.6 WOG, initial Manning fetal biophysical profile assessment of less than 8 points, or fetal pre-existing diseases or malformations.

Study groups. This was an experimental longitudinal prospective study in which 100 pregnant women from the General Hospital of Ciudad Victoria "Dr. Norberto Treviño Zapata" were enrolled. Study Group 1 (control group) consisted of 50 patients whose first visit to the hospital was during labor and referred no previous prenatal care or had any anti-anemic treatment. Of these, 20% ($n = 10$) were diagnosed with anemia (Group 1b) with a CBC resulting in a prevalence slightly higher than the national average. 50 women diagnosed with iron deficiency anemia through CBC, who accepted therapeutic management, were randomly assigned to treatment groups. In group 2, 25 third trimester women in between 31 and 35.5 WOG with a hemoglobin concentration of <11 mg/dL were recruited and treated with 600 mg of ferrous sulfate (195 mg of elemental iron) administered orally daily for four weeks. These patients underwent maternal and fetal assessment every week evaluating hematological changes in the mother, registering the fetus' weight and growth through non-stress tests and mean ultrasound fetometry (Ultrasound Voluson E8 Expert. General Electric Healthcare). In group 3, 25 women similar to group 2 were recruited and treated with the same dose of ferrous sulfate, but adding 4000 units of rHuEPO subcutaneously 3 times per week during the same period. The same maternal and fetal parameters were registered. At the moment of birth, a sample was obtained from the mother for a CBC, and another for the infant, obtained from the umbilical cord blood.

Blood samples. Hematological variables from every same were analyzed, including hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet count (PLT), and white blood cells (WBC).

Parameters. Completion of treatment was established when the mother showed a hemoglobin concentration over 12 g/dL. If at any point, the fetus demonstrated restricted intrauterine growth or adverse effects, rHuEPO administration was suspended.

Statistical analysis was performed using SPSS version 20 software package (Statistical Package for the Social Sciences. IBM). Descriptive statistics were obtained with significance value set a 95% (p 0.05).

Ethical considerations. This study was reviewed and approved by the Ethics Committee, certifying that it adheres to the guidelines of the General Health Law on Health Research in Human Beings of our country and the Helsinki declaration. Informed consent from all patients was obtained. The authors declare no conflicts of interest.