# Treatment of anemia of chronic disease with true iron deficiency in pregnancy

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**Study population and criteria**

Fifty anemic pregnant women with moderate anemia were prospectively observed and treated in the Anemia clinic at the Department of Obstetrics, University Hospital Zurich. All patients had singleton pregnancies. All pregnant women fulfilled criteria of moderate iron deficiency anemia defined as hemoglobin between 8.0 and 9.9 g/dl and serum ferritin <15 µg/l. In all women, the analyses of a blood count, iron status, erythropoietin, cross reactive protein (CRP), folic acid and vitamin $B_{12}$ were conducted.

Primary endpoint was the assessment and comparison of the efficacy of anemia treatment in pregnant women with iron deficiency anemia and anemia of chronic disease with true iron deficiency.

Secondary endpoint was the target hemoglobin ≥10.5 g/dl.

Exclusion criteria were anemia of other etiology (i.e. vitamin $B_{12}$ deficiency, folic acid deficiency, hemoglobinopathy etc.), liver or kidney disease, and multiples. Women with mean corpuscular hemoglobin (MCH) ≤25 pg, mean corpuscular volume (MCV) ≤75 fl; and percentage of microcytic erythrocytes (MRC) ≥3% were tested for hemoglobinopathies.

Flow cytometry was used to determine the total iron demand of erythropoiesis by measuring HRC, CHr, and RDW. Iron deficiency anemia is defined as anemia with depleted iron stores and with elevated levels of HRC >2.5%, decreased CHr <28 pg and elevated RDW >15%. In combination with the indicators of erythropoiesis (hemoglobin, red blood cells and hematocrit) as well as the indicators of iron household (serum ferritin and transferrin saturation), we identified anemia of chronic disease with reduced iron stores but with normal level of hypochromic erythrocytes (HRC <2.5%), normal reticulocyte hemoglobin content (CHr >28 pg)), normal red blood cell distribution width (RDW <15%) and low serum EPO levels for the grade of anemia (serum EPO <50 U/l by Hb <10 g/dl).

**Laboratory assessment**

Hb, red blood cells (RBC), hematocrit (HCT), MCV, MRC, HRC, RDW, CHr were measured using an ADVIA® hematology analyser system (Bayer Diagnostics, Leverkusen, Germany). MCH was automatically calculated from Hb and RBC. Iron status was assessed by chemiluminescence–immunoassay (ACS 190; Ciba/Corning Diagnostic Corp., Cleveland, OH) of serum ferritin, iron and transferrin. Transferrin saturation was calculated as 100 x iron/2 x transferrin. Radioimmunoassay was performed to determine vitamin $B_{12}$, folic acid and the levels of serum EPO. CRP was assessed through immunoturbidimetry. The hematological parameters were checked twice a week in the anemia clinic and iron status once a week.

**Therapy protocol**

According to hemoglobin level at the start of the therapy, the women were either treated with intravenous iron and rhEPO or with intravenous iron only twice weekly as described elsewhere. Patients with an Hb level between 9.0 and 9.9 g/dl (33 patients) received 200 mg iron sucrose (VENOFER®, Vifor Int., St. Gallen, Switzerland) intravenously twice weekly. If response to therapy was poor (i.e. Hb increase <0.7 g/dl) after 2 weeks (13 patients), patients additionally received rhEPO (10,000 U EPREX®, Janssen-Cilag, Baar, Switzerland). This cut-off for adequate primary response we choose on the basis of our previous experience. Patients with an Hb between 8.0 and 8.9 g/dl (17 patients) received iron sucrose (Venofer) and rhEPO (Eprex) twice weekly from the start of therapy.

Sufficient overall response to therapy (the difference of baseline hemoglobin and after therapy) was defined as Hb increase >1.0 g/dl. The maximum total iron dose was 1,600 mg, therefore therapy was stopped if the maximal iron sucrose dose was administered, or target Hb > 10.5 g/dl was achieved.

Side-effects (hypotensive and hypertensive response, allergic reaction, thromboembolic complications) were registered.

**Statistical analysis**

All statistical analyses were performed using the statistic program STATA 8 (Stata Corporation College Station, TX). $P<0.05$ was considered statistically significant. Baseline characteristics were compared using Mann-Whitney and Chi-square tests when appropriate.