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Iron Deficiency and Anaemia in Pregnancy: Modern Aspects of Diagnosis and Therapy

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ABSTRACT: The prevalence of iron-deficiency anemia in different regions of the world ranges from 12 to 43%. The increased iron requirement in pregnancy and the puerperium carry with it an increased susceptibility to iron deficiency and iron-deficiency anemia and perioperative or peripartal blood transfusion. Prevention and correction presuppose reliable laboratory parameters and a thorough understanding of the mechanisms of iron therapy. The Hb level alone is insufficient to guide management. A complete work-up (ferritin, transferrin saturation) is essential, preferably with hematological indices such as hypochromic and microcytic red cells and reticulocytes, classified by degree of maturity, in particular, before parenteral therapy is given. Since ferritin acts as both an iron-storage and acute-phase protein, it cannot be used to evaluate iron status in the presence of inflammation. A high ferritin level thus requires the presence fo an inflammatory process to be eliminated before it can be taken at face value. If the C-reactive protein level is also raised, the soluble TfR concentration can be used, since it is unaffected by inflammation. Inadequate understanding of the complex chemistry of parenteral iron administration was previously responsible for serious side effects, such as toxic and allergic reactions, and even anaphylactic shock, in particular with dextran preparations. However, the current type II iron complexes that release iron to the endogenous iron-binding proteins with a half-life of about 6 hours are not only effective but carry a minimal risk of allergic accident and overload, especially after a comprehensive pretreatment work-up. Our departmental data collected over 8 years and backed by postmarketing experience in 25 countries indicate that iron sucrose complex therapy is a valid first-line option for the safe and rapid reversal of iron-deficiency anemia.

Key Words: pregnancy-anaemia-iron-transferrin receptor-hypochromic red cell

INTRODUCTION

Anaemia during pregnancy is a well known and considerable risk factor for both mother and fetus (Table 1). Fetal consequences are an increased risk of growth retardation, prematurity, intrauterine death, amnion rupture and infection. Prematurity is a consequence of early anaemia during gestation which leads to release of placental stress hormones (CRH, Norepinephrine) which induc fetal release of ACTH and cortisol. These induce production of uterine contraction stimulating hormones (estrogen, connexin) and inhibition of insulinlike growth factor (IGF), an important anabolic hormone for fetal development (1). It was also shown that placental development is influenced by anaemia and hypoxia, e.g. as causes of abnormal trophoblast invasion and release of hypoxia inducible factor (HIF) as a consequence. Abnormal feto-placental development is an underlying cause of several problems of the newborn and adult life as described by "fetal-programming" (2).

Maternal consequences of anaemia are also well known and include cardiovascular symptoms, reduced physical and mental performance, reduced immune function, tiredness, reduced peripartal blood reserves and finally increased risk

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TABLE 1

Fetal and Maternal Consequences of Anemia in Pregnancy

Fetus/Placenta	Maternal
—Prematurity	—Reduced blood reserves
—Premature contractions	—Low exercise and mental performance
—Amnion rupture	—Cardiovascular strain
—Growth retardation	—Tiredness
—Abnormal trophoblast invasion	—Reduced immune function
—Fetal programming	—Infection
—Diseases in newborn	—Negative Thermoregulation
	—Increased risk of blood transfusion

TABLE 2

Development of Iron Status Testing

Blood smear	1889
Erythrocyte indices	1897
Serum Iron	1937
Bone marrow	1948
Ferritin	1972
EC Scattergram	1984
Transferrin Receptor	1986

for blood transfusion in the postpartum period. For clinical management, proper diagnosis and therapy are mandatory to reduce maternal and fetal risks and to enable optimal obstetrical outcome of both (3).

DIAGNOSIS

Knowledge of different haemoglobin cut off levels during pregnancy to differentiate between hydraemia and true anaemia is important in the first step of diagnosis. According to the Centers of Disease Control data from 1989, lower haemoglobin cut off is 11.0 g/dL in the first and last trimester and 10.5 g/dL in the second trimester. Therefore any level below 10.5 g/dL should be regarded as anaemia and consequently checked.

The next step includes differential diagnosis of anaemia. Iron deficiency the major cause of anaemia during pregnancy, but others such as infection, abnormal haemoglobin, renal disease or parasites (malaria, worms) must be ruled out before therapy starts to guarantee optimal thereapeutic effects (4).

LABORATORY PARAMETERS

In addition to clinical assessment, laboratory parameters are of major importance for differential diagnosis of anaemia. More than 100 years ago first tests including blood smear, red cell

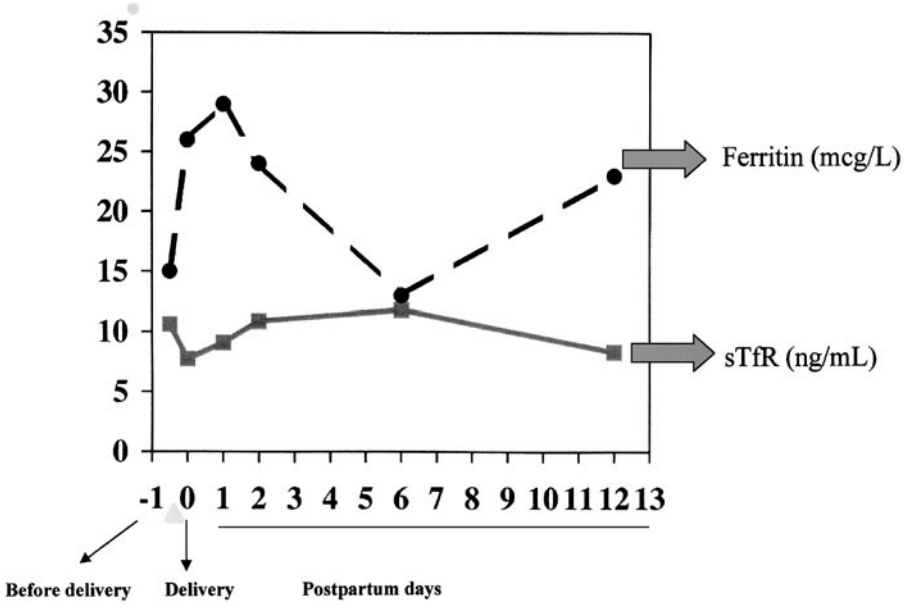

FIG. 1. Course of ferritin and serum transferrin receptors (sTfR) in a *pre-term* iron deficient patient treated with oral iron post partum. Iron deficiency was diagnosed before delivery to exclude false normal ferritin values. Note how ferritin levels are influenced by delivery inflammatory reaction, while sTfR essay is not.

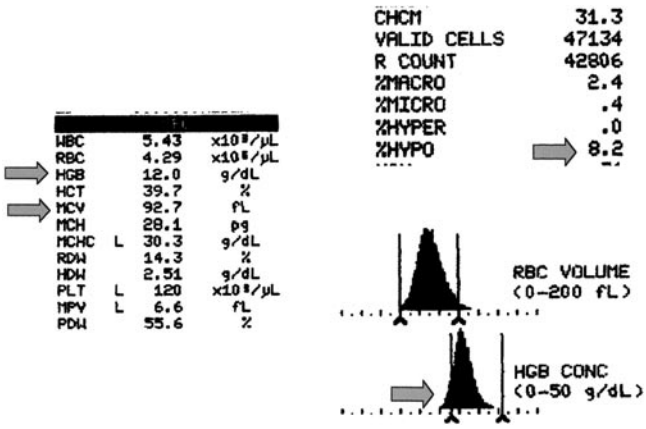

FIG. 2. Red cell analysis using a hematologic analyzer that measures hypochromic red cells by flow cytometry. This pregnant patient has a normal haemoglobin and MCV in first trimester. However hypochromic red cells (% Hypo right panel) are already 8.2%, also indicated by a rightward shift in the scattergramm. This indicates latent or functional iron deficiency before iron deficiency anemia has developed. This patient will benefit from iron supplementation.

indices and serum iron have been introduced. Later bone marrow stain and most important serum ferritin test have been introduced, ferritin being the actual gold standard of iron status testing (Table 2). However, in certain conditions such as underlying infections, ferritin is not valuable, since it reacts as a acute phase reactant and shows false normal results, e.g. in the postpartum period (Fig. 1). During pregnancy, ferritin shows also weak correlations to other iron parameters and the severity of anaemia, therefore additional tests are helpful (5, 6).

Hypochromic Red Cells

Hypochromic red cells are released into the blood in cases of severe anaemia, e.g. iron deficiency, or during functional iron deficiency, e.g. erythropoietic stress with insufficient iron supply (7). Using modern automated red cell analyzer systems it is possible to measure the quantity of hypochromic red cells (HRBC) and the percentage of HRBC of total red cells. These data are helpful to determine the severity of iron deficiency, for differential diagnosis (e.g. thalassaemia vs. iron deficiency) of anaemia, for the

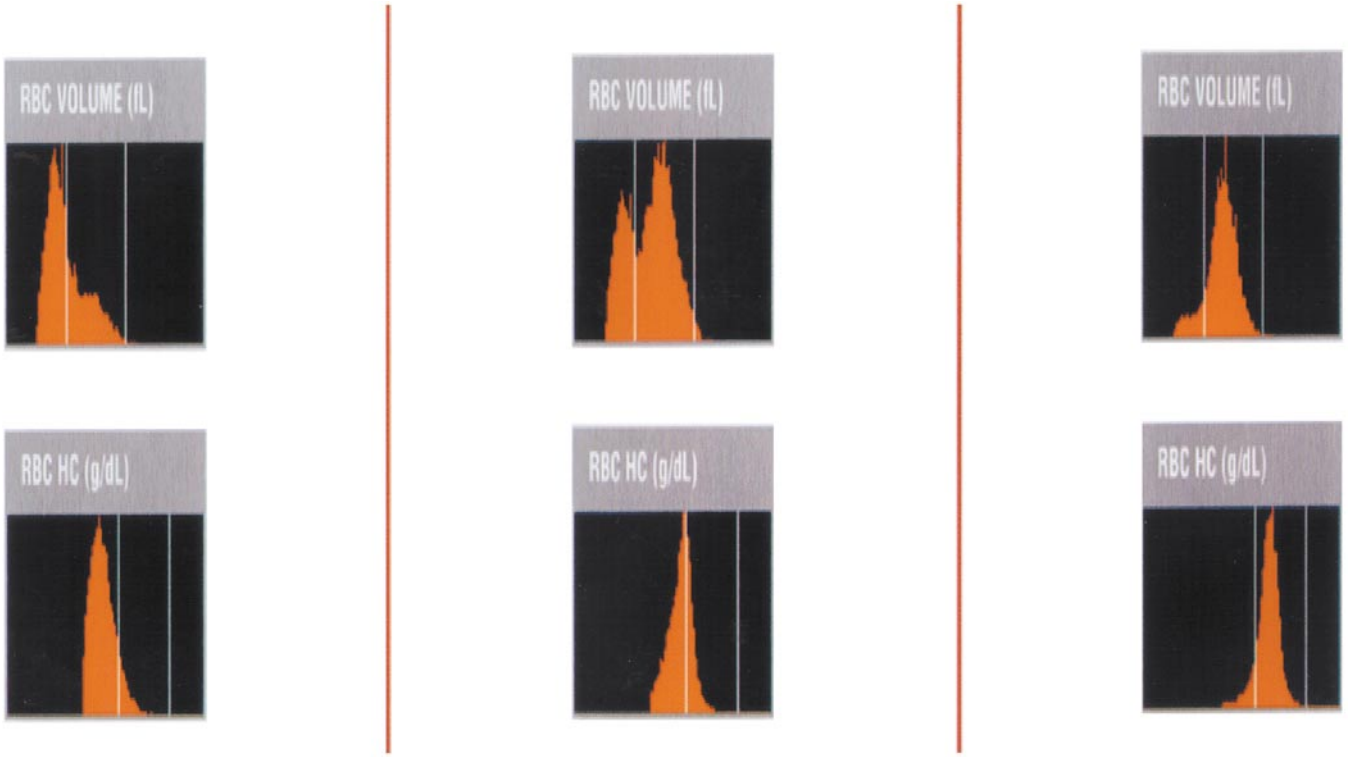

FIG. 3. Assessment of hypochromic red cells using scattergarmms during therapy of severe anemia in a pregnant patient. Note how percentage of HRC decreases during normalization of anemia. Patient refused blood transfusion and was treated with parenteral iron sucrose.

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TABLE 3

Characteristics of Iron Sucrose Complex

- Iron (III) hydroxide sucrose complex (Venofer®)
  - —High safety
  - —Low tissue accumulation
  - —High stability
  - —High availability for erythropoiesis
  - —Rapid incorporation (bone marrow and red cells)
  - —Prevents iatrogenic iron depletion (e.g. after rhEPO)

assessment of functional iron deficiency (e.g. during rhEPO treatment) and finally the monitoring of therapy and its effects, namely decrease of hypochromics due to efficient iron administration.

Fig. 2 gives an examples of diagnosis of latent iron deficiency or beginning functional iron deficiency in early pregnancy, while Fig. 3 presents therapy monitoring using HRBC during treatment of severe anaemia during pregnancy.

Soluble Serum Transferrin Receptors

Serum transferrin receptor (sTfR) essay is another important new laboratory test which is increasingly used in obstetrics (8). STfR are on the surface of every iron incorporating cell and are released into the blood in cases of increased tissue iron needs such as during severe iron deficiency or during forced erythropoiesis. As HRBC, increased sTfR levels indicate functional iron deficiency but also increased erythropoiesis and body iron needs. STfR are not influenced by inflammatory processes, therefore this test is most valuable if interpretation of ferritin alone is difficult (s.a. Fig. 1) such as in the postpartum period. It has been shown that surprisingly postpartum sTfR are low, despite increased iron needs which in this case might reflect suppressed erythropoiese of unknown origin.

Further examples of the use of HRBC and sTfR essay will be given later in the text.

THERAPEUTIC OPTIONS

Traditional therapeutic options of iron deficiency anaemia in pregnancy were administration of oral iron or in severe cases administration of blood transfusion. While oral iron shows limited effectiveness in cases of severe anaemia due to various factors such as side effects, lack

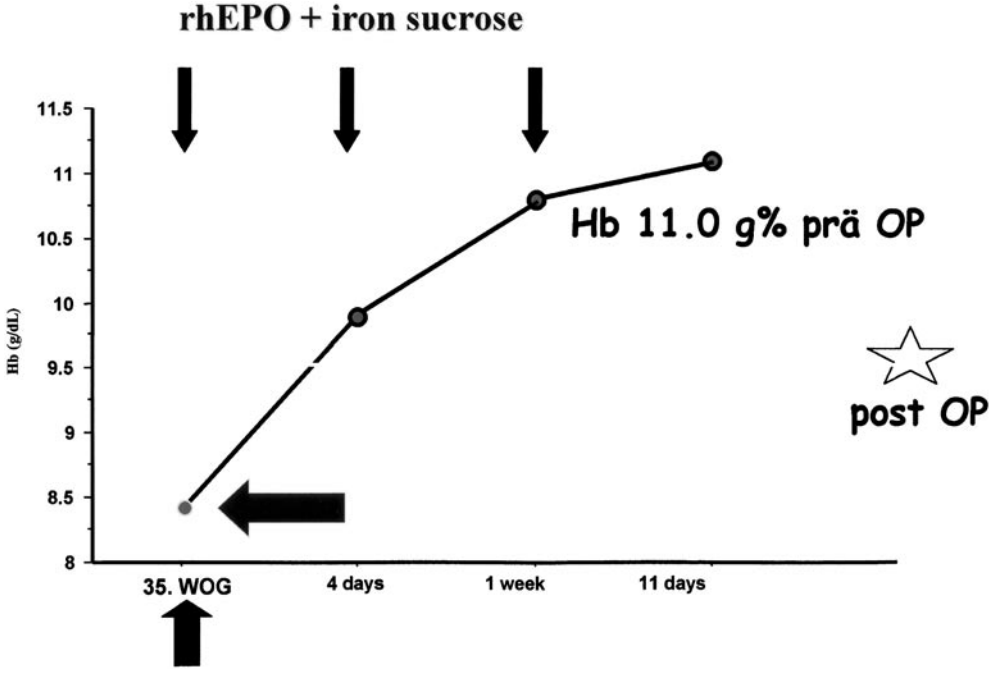

FIG. 4. Use of rhEPO and iron sucrose in a Jehovah′s whitness with severe anemia prior caesarean section. Treatment starts at 35 WOG After 11 days Hb of 11.0 g/dL is reached. Despite blood loss >1000 mL, the patient has no critical Hb post operatively (9.5 g/dL).

TABLE 4

Groups Before Therapy

	rhEPO + Iron sucrose IV	Iron sucrose
WOG	31.6 (22–38)	31.7 (21–38)
Hb (g%)	9.0 ± 0.7 (7.9–9.9)	9.2 ± 0.6 (8.2–9.9)
Hk (%)	28.3 ± 2.5 (24.8–32.5)	29.3 ± 1.9 (25.5–32.8)
Ferritin (μg/dL)	7.5 ± 4.8 (2.0–15.0)	7.1 ± 4.3 (2.0–15.0)
Hypochromic EC (%)	14.5 ± 12.6 (1.0–46.0)	18.2 ± 10.3 (3.6–39.9)
EPO-Level (U/L)	75.9 ± 12.1 (12.7–207)	85.5 ± 61.0 (22.9–193.0)
CRP (mg/dL)	4.4 ± 2.1 (3.0–10.0)	4.6 ± 2.5 (3.0–11.0)

of compliance and often limites intestinal absorption and bioavailability (9), blood transfusion must be avoided due to considerable transfusion risks such as infections, risk of incorrect transfusion, transfusion reactions and nagative impact on the immune system. There is also an increasing number of patients who deny blood transfusion (10–12).

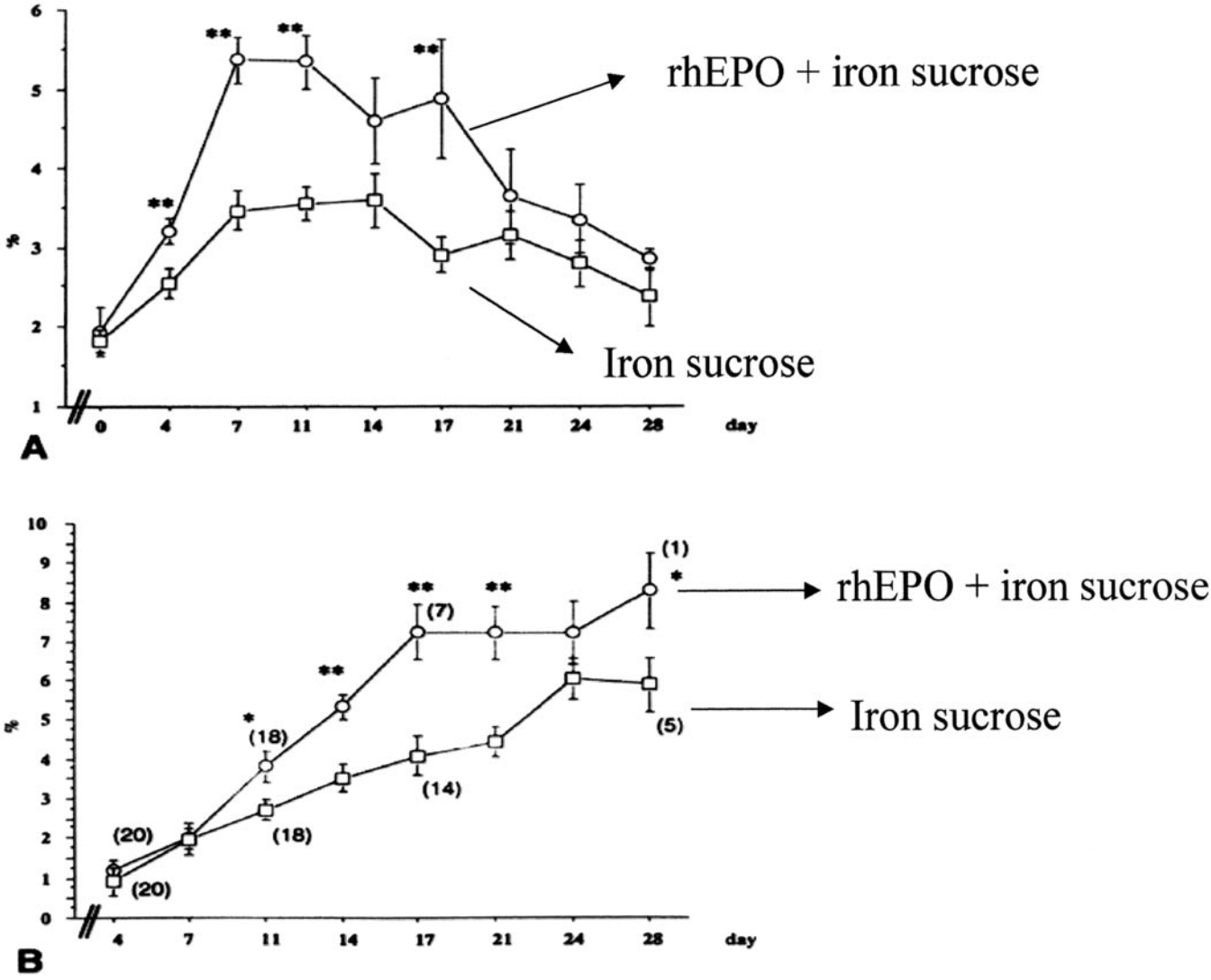

FIG. 5. Course of reticulocyte counts and change in haematocrit in patients with anemia in pregnancy who receive either rhEPO and iron or Iron sucrose only (dosages see text).

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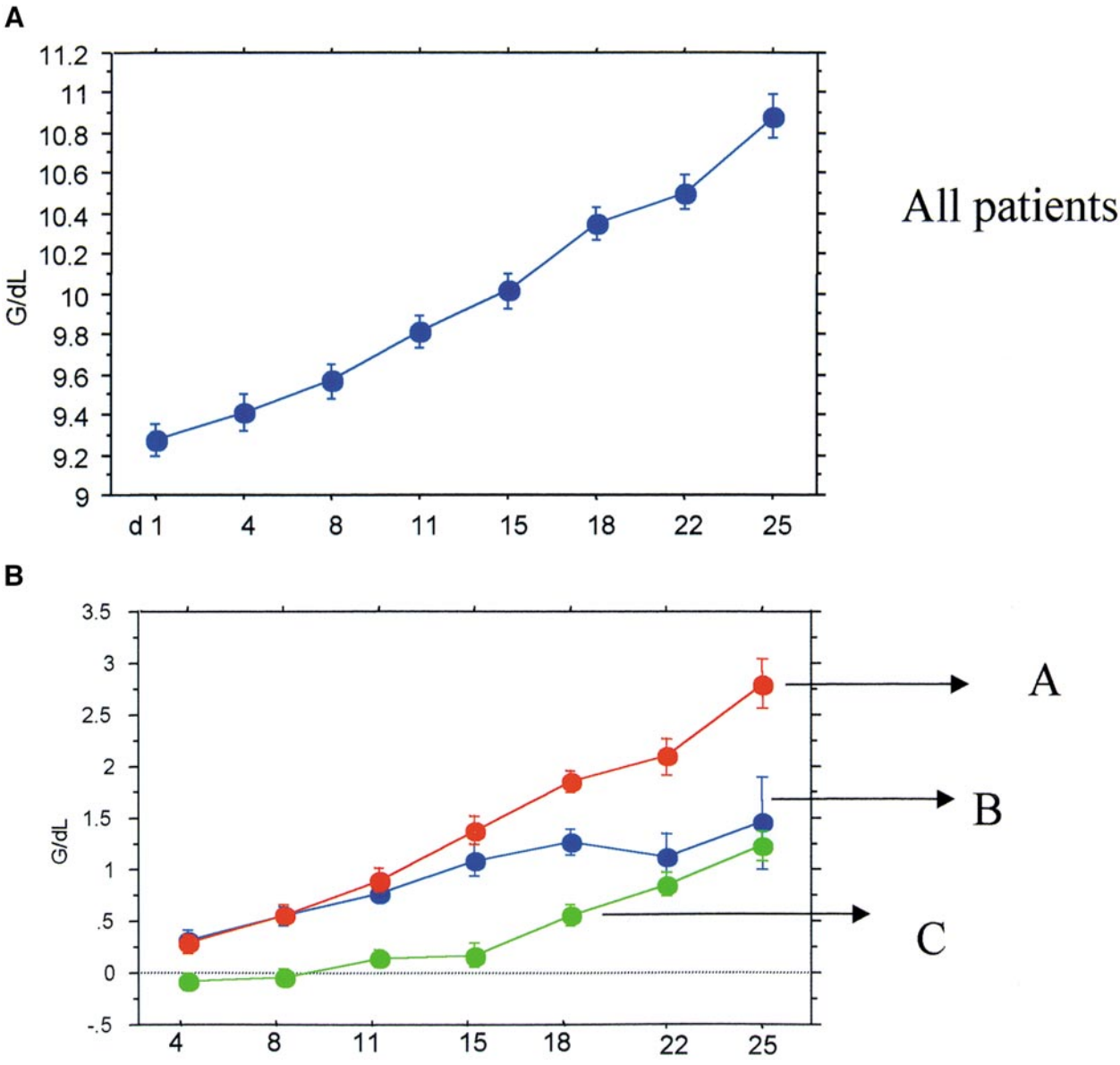

FIG. 6. Ongoing trial of treatment of severe anemia in pregnancy. 6A shows Hb course for all patients while 6B shows subgroups, treated either with a combination of rhEPO + iron sucrose complex (A) (Hb < 9.0 g/dL) or iron sucrose complex only (B) (Hb > 9.0 g/dL). If patients from group B (>9.0 g/dL) do not respond to iron sucrose only, additional rhEPO is given (C). Note how the haemoglobin starts to increase thereafter. A shift from group B to C is seen in nearly half of the patients.

ALTERNATIVES

Recently there is increasing interest on alternative therapeutic options which include use of parenteral iron sucrose complex (Table 3) and recombinant human erythropoietin (13–16).

Parenteral iron sucrose complex has several advantages because it has a low allergenic properties with an extrmely low incidence of severe side effects such as anaphylactic reactions (17, 18). We have recently shown the safety profile in pregnancy with a frequence of general side effects of 0.36% in 400 patients (2700 ampoules). Meanwhile we have treated additional 500 patients with same safety results (19). In addition iron sucrose complex has a high availability for erythropoiesis, little renal excretion (<5%) and low tissue accumulation and toxicity. It is also the preparation of choice for treatment and prevention of functional iron deficiency, e.g. during use of rhEPO (20).

Recombinant human erythropoietin (rhEPO) is an erythropoietic growth factor which induces

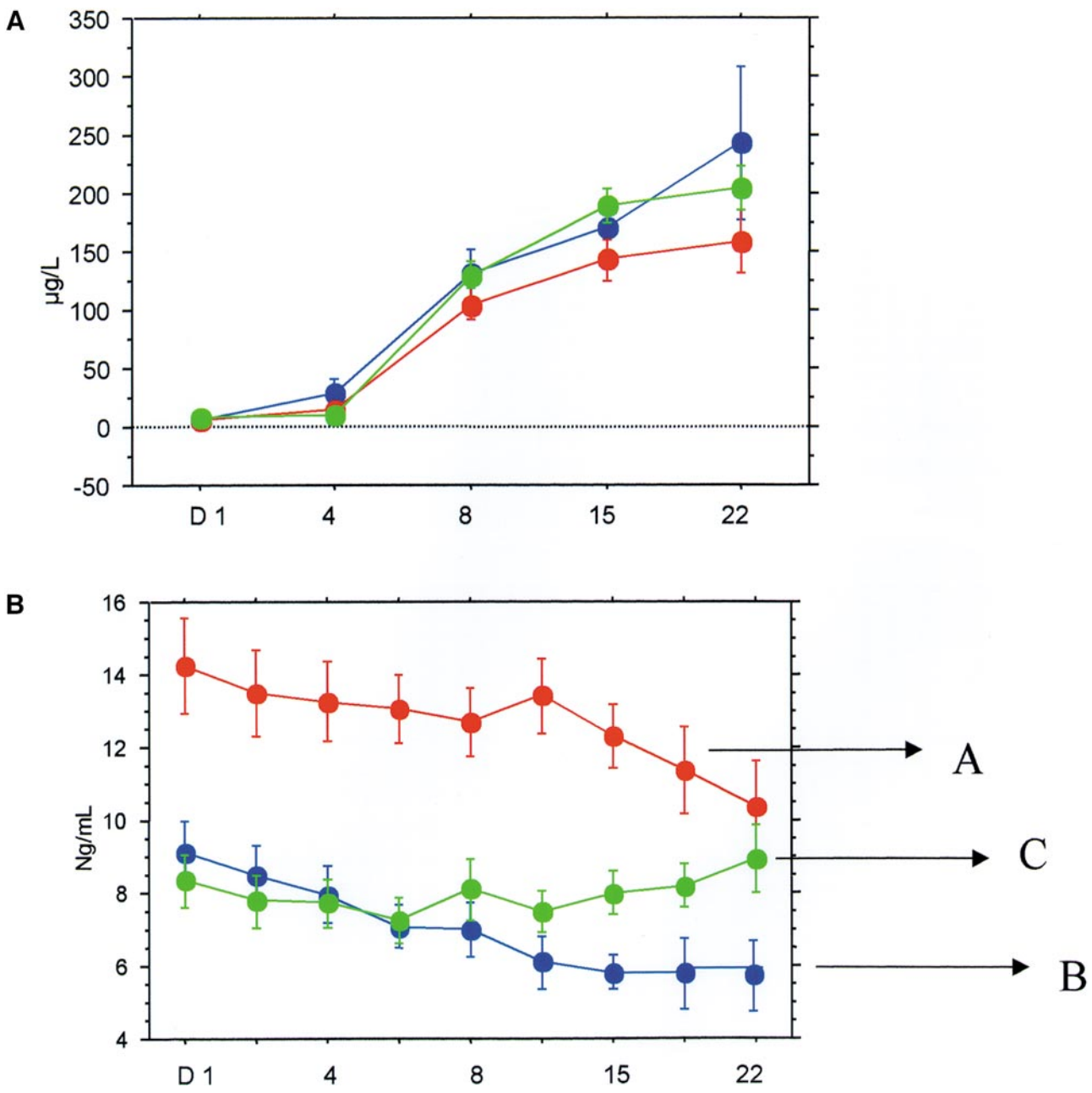

FIG 7. Course of ferritin (A) and sTfR (B) in the subgroups. (A) rhEPO + iron sucrose from start of therapy, (B) iron sucrose only, (C) First iron the start of rhEPO after 14 days (non-responders to iron).

proliferation and differentiation of erythroid precursor cells and prevents their apoptosis.

RhEPO has been used for anaemia treatment since the late 80′s and has also been used in obstetrics with excellent results, e.g. in patients with renal anaemia in pregnancy, Jehovah′s whitnesses, pre- and postoperatively and in the postpartum period (15, 21, 22). Fig. 4 shows an example of a Jehovah′s whitness with placenta praevia and anaemia before caesarean section, who was treated with rhEPO and iron. According to our experience and others use of parenteral iron is mandatory if rhEPO is used, to prevent iatrogenic iron depletion and functional iron dficiency during treatment. This improves also cost-effectiveness of rhEPO, since by optimizing iron administration, rhEPO dosage can be reduced.

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TABLE 5

Baseline Data for Anemic Pregnant Patients Before Therapy

	Mean	Std. Dev.	Std. Error	Count	Minimum	Maximum
WOG	28.659	7.204	1.086	44	14.000	41.000
Hb (g/dL)	9.278	.653	.081	65	7.400	10.400
MCV (fL)	79.364	7.660	.958	64	63.600	96.800
Tf.sat. (%)	11.232	10.259	1.293	63	1.961	52.083
EPO (U/L)	60.970	41.578	5.238	63	10.000	168.000
MRC (%)	9.206	10.629	1.339	63	.200	41.800
HRC (%)	13.800	14.182	1.787	63	.200	51.700
sTfR (ng/mL)	10.410	4.752	.647	54	2.417	26.599
Ferritin (μ/L)	6.723	3.603	.447	65	2.000	15.000

USAGE OF rhEPO and IRON SUCROSE-DATA FROM OUR OWN EXPERIENCE

Patients

We present data from a randomized trial comparing iron sucrose vs rhEPO and iron sucrose in patients with iron deficiency anaemia during pregnancy (22). These patients were treated primarily with oral iron for a minumum of two weeks without success. Other reasons causing anaemia were excluded.

Methods

Patients were randomized and treated with either iron sucrose (200 mg i.v.) alone ore iron sucrose (200 mg i.v.) and rhEPO (300 U/ kg b.w. i.v.) twice weekly. Target haemoglobin was 11.0 g/dL, if this was reached treatment was stopped (for further reading see (23)).

Results Shown

Table 4 shows baseline data of the two groups with no differences prior therapy.

Fig. 5 shows published results of reticulocyte increase and haemotocrit increase in the groups. It was shown that combination of iron sucrose with rhEPO results in higher reticulocyte and haemoglobin increases compared to iron alone. After 4 weeks all but one patients had reached target haemoglobin levels in the iron/rhEPO group vs five patients in the iron only group.

ONGOING STUDY (rhEPO/IRON SUCROSE)

Patients

We have now initiated a new study with patients treated with either iron sucrose alone, if haemoglobin before therapy is over 9.0 g/dL or iron sucrose (200 mg, i.v., twice weekly) and rhEPO (300 U/kg b.w., i.v., twice weekly) if Hb is below 9.0 g/dL. In addition patients who do not respond to iron after 14 days receive additional rhEPO (dosage as above).

Results

Table 5 shows baseline data of the collective, note elevated levels of HRBC (normal $<$ 2.5%) and sTfR (normal $<$ 8.5 ng/mL). All patients have abnormal ferritin levels.

Fig. 6A shows haemoglobin increase for the whole collective while Fig. 6 shows the corresponding subgroups. It can be seen how patients primarily treated with rhEPO and iron sucrose ($<$9.0 g/dL) show a steady increase in haemoglobin as doe some patients with iron only. Howevere there is a considerable number of patients who do not respond to iron only but only to the combination of rhEPO/ iron.

While ferritin levels and transferrin saturation increase during treatment, assessment of sTfR and HRBC reveals different iron kinetics in the patients (Fig. 7). All patients have elevated levels of sTfR and HRBC prior therapy but patients with

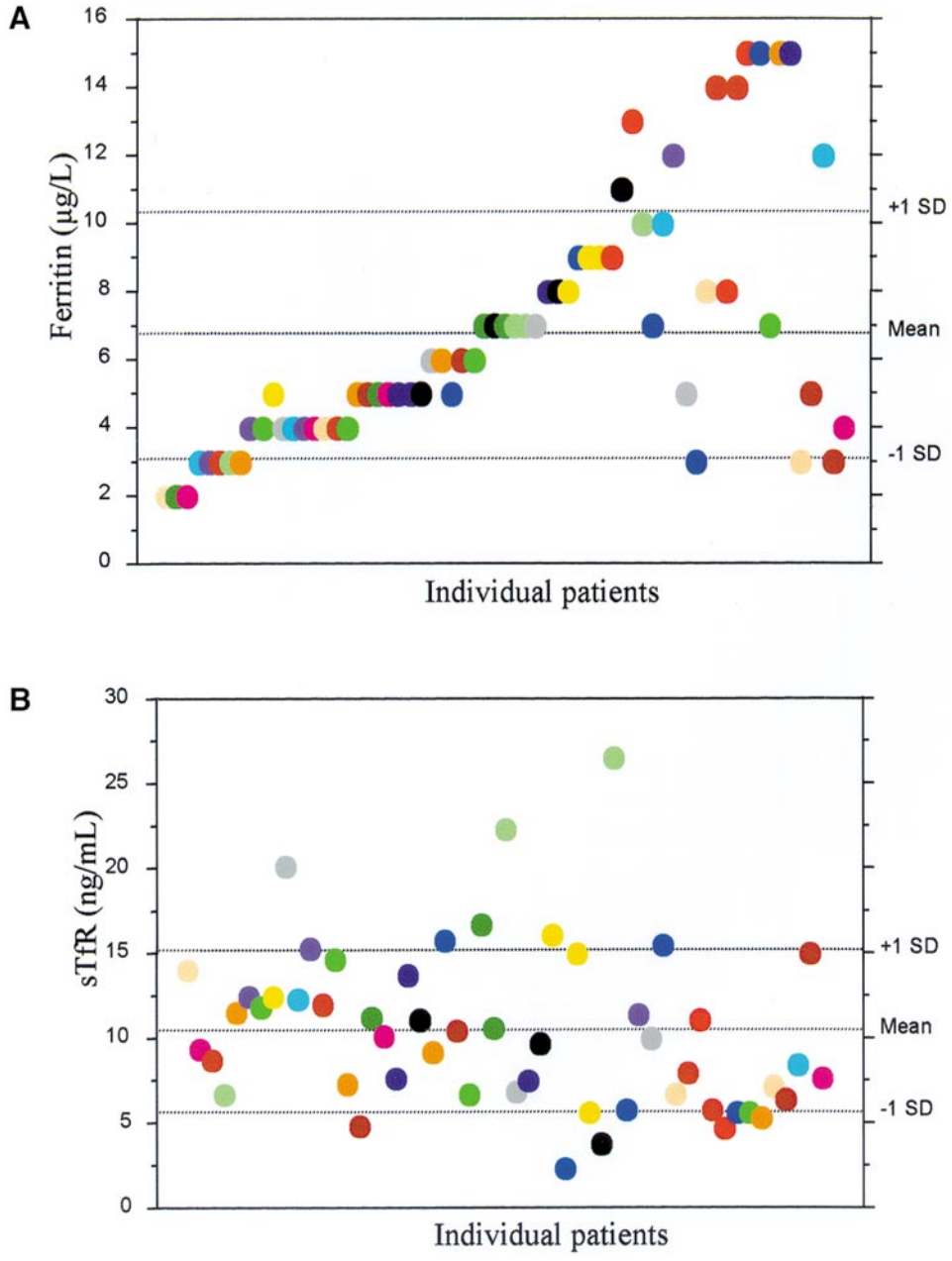

FIG. 8. Point scattergram of individual patients with anemia in pregnancy. 8A: distribution of ferritin levels, 8B: distribution of sTfR Prior therapy. Note that a considerable number of patients shows normal sTfR levels (<8.5 ng/mL) despite severe iron deficiency according to ferritin levels.

severe anaemia show considerably elevated levels of both sTfR and HRBC (data not shown).

During treatment levels of HRBC decrease slowly in all groups which shows the effect of iron sucrose. Also sTfR levels decrease in those patients treated with rhEPO/ iron primarily or those who respond to iron only. However those who are non-responder to iron only show an increase of sTfR levels after start of rhEPO due to the effect on erythropoiesis (Fig. 7B).

This data show nicely how it is possible to discriminate between therapy response using these new parameters while ferritin and transferrin saturation allow no discrimination between severity of anaemia and response.

Fig. 8 shows point charts of individual patients and their distribution concerning various iron parameters. All patients are anaemic and in respect to ferritin levels iron deficient. However regarding sTfR and HRBC (data not shown) it can be shown,

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that many patients have normal levels of both sTfR and HRBC. Serum EPO levels are low for the grade of anaemia in most patients (data not shown).

DISCUSSION

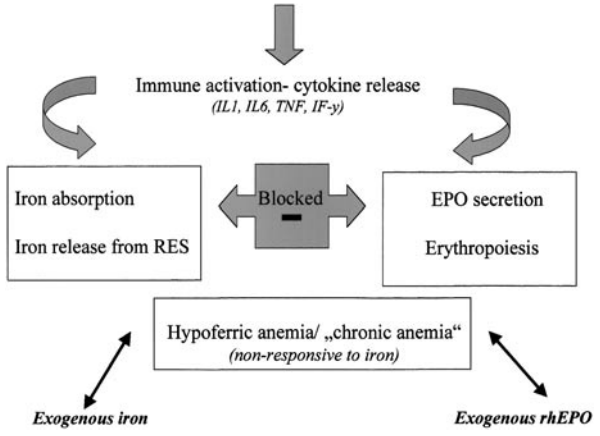
In these preliminary data we show that a combination of iron sucrose and rhEPO is most effective in treating anaemia during pregnancy. This confirms the results from the previous randomized trial (23). We have now investigated subgroups of patients and their response to intensive therapy and it can be shown that there are responders to iron only and responders to the combined therapy (iron/ rhEPO). Finally there is a considerable number of patients with no response to iron only, which would be expected after two weeks of parenteral iron in "classic" iron deficiency anaemia. In respect to new parameters such as transferrin receptors and hypochromic red cells it seems that there is a considerable number of patients which do not fullfil classic criteria of iron deficiency anaemia, namely low ferritin, transferrin saturation and haemoglobin, because they show also normal sTfR levels and normal numbers of HRBC. Finally most patients have low EPO levels and a lack of strong correlation between EPO and haemoglobin. This leads us to the concept of hypoferric anaemia in pregnancy which is a subtype which has criteria similar to anaemia of chronic disease: low EPO levels and suppressed erythropoiesis and inhibited iron incorporation (Table 6). We are now investigating possible reasons for this observation such as increased cytokine leves during pregnancy due to inflammatory processes which might lead to this phenomenon.

CONCLUSION

Anaemia during pregnancy and its management remains an important issue in perinatal medicine. Correct diagnosis and treatment lead to effective management of fetal and maternal risks and improved perinatal outcome. While new parameters such as hypochromic red cells and transferrin receptors enable correct differential diagnosis and therapy monitoring, new therapeutic options such as iron sucrose complex and rhEPO improve therapy effectiveness and safe outcome avoiding blood transfusion.

TABLE 6

Subclinical Infection/Chronic Inflammation During Pregnancy
(Viral ? Bacterial ? Amnioinfection ? Bacterial vaginosis ? Urinary tract ?)



Future investigation of iron metabolism in pregnancy should put an eye on interesting questions such as a possible hypoferric anaemia in pregnancy which was usually falsely regarded as pure iron deficiency anaemia in pregnancy.

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