Review article

Parenteral iron therapy in obstetrics: 8 years experience with iron–sucrose complex

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Fe is an essential component of haem in myoglobin and accounts for 70 % of haemoglobin. The balance of Fe, unlike that of other metals such as Na or Ca, is regulated solely by gastrointestinal absorption, which itself depends on the bioavailability of Fe in food, i.e. the chemical Fe species. Factors that maintain Fe homeostasis by modulating Fe transfer through the intestinal mucosa are found at the luminal, mucosal and systemic levels. Fe deficiency and its consequence, Fe-deficiency anaemia, form the commonest nutritional pathology in pregnant women. The current gold standard to detect Fe deficiency remains the serum ferritin value. Previously there was general consensus against parenteral Fe administration, i.e. parenteral Fe was only recommended for special conditions such as unresponsiveness to oral Fe, intolerance to oral Fe, severe anaemia, lack of time for therapy etc. However, especially in hospital settings, clinicians regularly face these conditions but are still worried about reactions that were described using Fe preparations such as Fe–dextrans. A widely used and safe alternative is the Fe–sucrose complex, which has become of major interest to prevent functional Fe deficiency after use of recombinant erythropoietin Numerous reports show the effectiveness and safety of the Fe–sucrose complex. Good tolerance to this Fe formulation is partly due to the low allergenic effect of the sucrose complex, partly due to slow release of elementary Fe from the complex. Accumulation of Fe–sucrose in parenchyma of organs is low compared with Fe–dextrans or Fe–gluconate, while incorporation into the bone marrow for erythropoiesis is considerably faster. Oral Fe is only started if haemoglobin levels are below 110 g/l. If levels fall below 100 g/l or are below 100 g/l at time of diagnosis, parenteral Fe–sucrose is used primarily. In cases of severe anaemia (haemoglobin <90 g/l) or non-response to parenteral Fe after 2 weeks, recombinant erythropoietin is considered in combination. By using parenteral Fe–sucrose in cases of severe Fe deficiency, anaemia during pregnancy is treated efficiently and safely according to our results and rate of blood transfusion could be reduced considerably to below 1 % of patients per year.

Iron: Pregnancy: Parenteral

Iron function and requirements

Fe is an essential component of haem in myoglobin and accounts for 70 % of haemoglobin (Hb). It is thus a key player in O_2 binding and transport. It is also found in many electron-transferring enzymes in the redox system of the respiratory chain. Total body Fe in man is 4–5 g. Daily losses, e.g. in epithelial desquamation from the gastrointestinal tract or skin, are small. Excretion in urine, bile and sweat is negligible (Forth & Rummel, 1992). The normal daily Fe requirement is thus only 1 mg, increasing with physiological need, as in growth, pregnancy and blood loss: an additional 1000 mg Fe is required in pregnancy, and 0·5 mg Fe/ml blood loss (Letsky, 1995; Hercberg *et al.* 2000).

Iron absorption

The balance of Fe, unlike that of other metals such as Na or Ca, is regulated solely by gastrointestinal absorption,

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which itself depends on the bioavailability of Fe in food, i.e. the chemical Fe species. Factors that maintain Fe homeostasis by modulating Fe transfer through the intestinal mucosa are found at the luminal, mucosal and systemic levels. The interactions between the various Fe species and the brush-border membrane are critical to the effectiveness of absorption.

The speciation of non-haem Fe depends on both dietary composition and intestinal secretions (Perewusnyk & Funk, 1997). In particular, Fe-binding intestinal mucins prevent the hydrolysis of Fe and its precipitation at high pH (Conrad *et al.* 1991). Parenteral Fe administration circumvents this gastrointestinal regulatory mechanism.

Prevalence and consequences of iron deficiency

Fe deficiency and its consequence, Fe-deficiency anaemia, form the commonest nutritional pathology in pregnant women (Allen, 1997). The prevalence of Fe-deficiency anaemia in pregnancy in the developing world is 56 (range 35–75) %, *v.* 18 % in the developed world. The corresponding figures in non-pregnant women are 43 and 12 % respectively (Cook *et al.* 1994). The prevalence of Fe deficiency is much higher. Without adequate Fe supplementation, ferritin falls to subnormal levels towards the end of pregnancy even in the industrialized nations (Carriaga *et al.* 1991; Milman *et al.* 1994; Letsky, 1995).

Maternal Fe-deficiency anaemia is associated with low birth-weight and increases in preterm birth rate and perinatal mortality (Garn *et al.* 1981; Murphy *et al.* 1986); it may also irreversibly impair fetal neurological development (Baynes, 1994). Further consequences include reduced exercise tolerance, stomatitis (Cook & Lynch, 1981), structural and chemical changes to the hair, nails and skin (Sato, 1991), and impairment of thermogenesis, thyroid metabolism and catecholamine turnover (Beard *et al.* 1990*a,b*). Fe deficiency increases the absorption of other cations, leading to excessive levels of Pb and Al, with corresponding toxic effects (Baynes, 1994). The impact on immune function remains unelucidated.

Investigation of iron deficiency

The standard Fe status variables are serum ferritin, transferrin, Fe, and transferrin saturation, Hb, and the red cell indices, mean corpuscular Hb, mean corpuscular Hb concentration, and mean corpuscular volume, which are all decreased in Fe-deficiency anaemia. In the absence of interfering factors, Fe deficiency is defined by a serum ferritin $< 15\,\mu\text{g/l}$, Fe $< 11\,\mu\text{mol/l}$ and transferrin saturation $< 15\,\%$. Pregnancy anaemia is defined by Hb $< 110\,\text{g/l}$ in the first or third trimester or $< 105\,\text{g/l}$ in the second (Centers for Disease Control and Prevention, 1989).

When applying these guidelines and limit values it is important to bear in mind that they may reflect factors other than Fe status. Thus, ferritin is also an acute-phase protein, i.e. its levels increase independently of Fe status in fever, acute and chronic inflammation, and rheumatoid arthritis, as well as in acute or chronic liver disease. There is increasing debate over the relevance of pregnancy ferritin levels since they often correlate poorly with the

degree of anaemia and are affected by subclinical infections (Baynes, 1994; Allen, 1997; Breymann, 2000). Nor is transferrin an always reliable index, being decreased in inflammation, infection, malignancy, liver disease, nephrotic syndrome and malnutrition, and increased by pregnancy and oral contraceptives. Serum Fe is likewise decreased by infection, inflammation, malignancy and vitamin C deficiency, and increased by transiently increased Fe absorption, aplastic anaemia, ineffective erythropoiesis and liver disease, as well as being subject to large diurnal variation through being replaced several times each day.

These key variables can thus become unreliable during critical phases in obstetric management, e.g. the postpartum inflammatory response when the cumulative effect of pregnancy and puerperal blood loss often results in Fe deficiency demanding correction. A newly-studied variable, the transferrin receptor (TfR) concentration, has been introduced to diagnose Fe-deficiency anaemia reliably under these conditions (Punnonen *et al.* 1997; Krafft *et al.* 1999; Perewusnyk *et al.* 1999; Rusia *et al.* 1999). TfR is a transmembrane protein present on virtually all cells. Its concentration depends on the Fe requirements of the cell and on cell growth (two-thirds of all TfR are found in red bone marrow). The serum TfR concentration detects Fe deficiency at the cellular level. Soluble TfR represents only the detached, extramembranous, transferrin-complexed portion of the receptor. Its levels are proportional to the total number of receptors in the tissue. These factors underlie the use of TfR quantitation as a sensitive indicator of Fe deficiency, unaffected by infection or inflammation, and independent of sex, age, and pregnancy *per se*. It can be used to differentiate between Fe-deficiency anaemia and the anaemia of chronic disease. It is especially informative at low ferritin levels when Fe deficiency cannot otherwise be quantitated. The combination of TfR, ferritin and Hb provides a complete picture of Fe store and functional compartment status.

Neopterin, another interesting newly-studied variable, regulates erythropoietin production by suppressing expression of the erthyropoietin gene. The serum neopterin concentration is inversely proportional to the Hb concentration (Schobersberger & Jelkmann, 1995). Neopterin can thus be used to distinguish between Fe deficiency and inflammation as the cause of defective Hb synthesis.

General remarks on iron therapy

A healthy diet rich in vitamin C and animal protein, and poor in phosphates, oxalic acid and fat, helps to prevent Fe deficiency and supports treatment with Fe preparations. The goal of therapy is to administer enough Fe to correct the anaemia and replenish the Fe stores. The advantages and disadvantages of the various preparations and routes of administration should be carefully weighed before selecting the form of therapy.

In the first instance the choice is between oral and parenteral therapy. Under normal circumstances oral Fe is the treatment of choice since it is simple, effective, safe and cheap. It also relies on the natural mechanism regulating total body Fe, namely the holo-transferrin and apo-transferrin receptors determining the Fe content of the

intestinal cells (Umbreit *et al.* 1998). However, oral Fe can cause nausea, malaise, vomiting, pain, diarrhoea, and constipation, resulting in poor compliance. These side effects can be relieved by co-administration with food, although this may substantially decrease absorption, particularly of ferrous preparations. Slow-release preparations of Fe salts or Fe complexes, e.g. iron(III) polymaltose which interacts with neither food nor other drugs, help to maximize absorption and decrease side effects to the placebo level. The parenteral therapy option is dictated by:

inadequate gastrointestinal iron absorption;
intolerance to the requisite dose of oral iron;
the requirement for emergency supplementation;
contraindication to blood transfusion;
chronic blood loss exceeding the oral replacement potential;
combination with recombinant human erthyropoeitin

Parenteral iron therapy

Parenteral Fe circumvents the natural regulatory mechanism to deliver non-protein-bound Fe. Free Fe is a potential toxin and/or carcinogen, leading to the production of hydroxide radicals and stimulating the growth of transformed cells by inhibiting the defence system. It can also cause changes in cell membrane permeability, and even cell lysis, via peroxidation of cell membrane lipid. Free Fe induces so-called O_2 toxicity, although is now known to be pathological only in Fe overload (Danielson *et al.* 1996). For these reasons parenteral Fe therapy should not be attempted until complete Fe status has been determined. The Hb concentration alone is not enough. Once parenteral therapy has been decided, it is important to choose a suitable product and administer it slowly to avoid excessive blood concentrations of free Fe.

Parenteral iron preparations

Four groups of parenteral preparations are available, classified according to kinetic (labile *v.* stable) and thermodynamic (weak *v.* strong) criteria. They differ essentially in complex stability, molecular mass, toxicity, histology, pharmacokinetics and side effects.

The type I complexes include iron dextran and iron dextrin, both stable, strong complexes of over 100 000 Da, displaying high structural homogeneity and thus releasing their Fe only slowly and competitively to endogenous Fe binding proteins. The Fe enters the reticuloendothelial system. The half-life of Fe dextran elimination from plasma is 3–4 d. The Fe binds to transferrin and some re-enters the plasma, from where it is transported to the bone marrow and utilized for Hb synthesis. High complex stability and slow Fe release enable these complexes to be classed as clinically safe. Side effects from the Fe are highly unlikely. However, because the complexes have a very high molecular mass, they may cause allergic reactions in very rare cases. Even low molecular mass dextrans can react with specific antibodies and provoke an anaphylactic reaction. This danger is avoided by using dextrin (Danielson, 1998).

Type II includes Fe complexes of intermediate stability and strength such as iron (III) hydroxide–saccharate complex (iron–sucrose complex: Venofer®, Vifor, St Gallen, Switzerland), with molecular masses ranging from 30 000 to 100 000 Da, releasing Fe to the endogenous Fe-binding proteins with a half-life of about 6 h. The Fe is taken up mainly in the reticuloendothelial system and liver, by transferrin and apoferritin, and by the spleen and bone marrow. It is rapidly metabolized and is thus rapidly available for erythropoiesis. At a recommended therapeutic dose of 1–4 mg Fe/kg body weight or 100–200 mg Fe/d, injected slowly or infused with NaCl, the transport system is not overloaded and Fe ions do not appear. Complex stability and the Fe distribution profile make this group clinically safe. Moreover, as the complexes contain no biological polymers, anaphylactic reactions are highly unlikely (Danielson *et al.* 1996; Danielson, 1998; Hoigné *et al.* 1998).

Type III comprises labile and weak Fe complexes with molecular masses below 50 000 Da. Examples include iron (III) gluconate, iron (III) citrate and iron (III) sorbitol. Administration of iron (III) gluconate at the doses used with types I or II causes severe and extensive liver necrosis. Fe is deposited in the reticuloendothelial system, but in also the parenchyma, leading to radical-generating lipid peroxidation. Iron (III) citrate and iron (III) sorbitol have very low molecular mass (about 8700 Da) and are excreted very rapidly by the kidney. Only a very small amount of Fe can therefore be transferred to the Fe-binding proteins.

Type IV is a mixture of at least two complexes of different classes, releasing Fe to all types of protein so that quantitative binding to transferrin or apoferritin is possible only if very small amounts are administered. Excess Fe is bound to proteins such as albumin and subsequently metabolized.

Given the lability of type III and IV complexes and their pattern of Fe distribution, neither can be considered clinically safe. Toxic reactions can be expected even at low therapeutic doses, and intravenous use is not recommended (Danielson *et al.* 1996; Danielson, 1998; Hoigné *et al.* 1998).

Experience with iron–sucrose complex in the department of obstetrics, Zurich university hospital (1992–2000)

Indications for parenteral therapy

The indication in pregnancy was the failure of Fe-deficiency anaemia (Hb < 100 g/l, ferritin < 15 µg/l) to respond by an increase in either reticulocytes or Hb to oral Fe (160 mg/d for 2 weeks). This presumed the pretreatment exclusion of other causes of anaemia, e.g. haemoglobinopathy, gastrointestinal bleeding, infections and vitamin B_{12} or folate deficiency (Breymann *et al.* 2001).

In line with WHO criteria (World Health Organization, 1972), the postpartum indication was Hb < 100 g/l after blood loss within 48 h of delivery (Breymann *et al.* 1996, 2000). Patients with Hb $> 10 \cdot 0$ g/l received oral Fe (80–160 mg/d).

Administration

Fe-sucrose (Venofer®, Vifor) was administered as either a bolus (undiluted) or short infusion (in 200 ml Nacl (9 g/l)). Maximum cumulative doses were 800 mg postpartum (200 mg/d for 4 d) and 1600 mg in pregnancy (200 mg twice per week to a target Hb of 110 g/l or for a maximum of 4 weeks), administered via peripheral catheter over 30 min for short infusions (in-patients) and over 5–10 min for bolus injections (outpatients).

Results

Safety profile

Over an 8-year period (1992–2000) a total of 500 patients received a total of 2500 ampoules, each containing the equivalent of 100 mg elemental Fe. Side-effect rates (flush (*n* 4) and rash (*n* 3)), all on the first day of treatment, were 1·5 % relative to the total number of patients and 0·36 % relative to the number of ampoules (Breymann, 1998; Hoigné *et al.* 1998). No serious side effects or anaphylactoid reactions were observed. In no case did treatment have to be discontinued or blood transfused due to non-response to treatment.

Pregnancy

Pretreatment mean Hb was 92 (SD 6) g/l (79–99 g/l) and gestational age 31·5 weeks (20–38 weeks). Mean treatment duration was 21 d (8–29 d). Both ferritin and transferrin saturation were clearly pathological at a baseline (7·0 (SD 4·0) μg/l and 6·2 (SD 3·7) % respectively). Hypochromic red cells levels were markedly elevated: 18·5 (SD 9·3) %. All variables improved significantly after 2 weeks (Table 1). Anaemia was corrected in all patients, with a mean increase in Hb of 19 g/l (significant from day 7, Fig. 1) and significant increases in mean corpuscular volume and mean corpuscular Hb. Hypochromic red cells fell by a mean value of 4·2 %. By the end of treatment, transferrin saturation and ferritin (also significant from day 7, Fig. 2) were normal.

Table 1. Response of haemoglobin, red cell indices, transferrin saturation and ferritin to parenteral iron–sucrose complex† in pregnancy iron-deficiency anaemia‡

(Mean values and standard deviations for 100 subjects)

	Day 0		Day 28		
	Mean	SD	Mean	SD	Normal value
Hb (g/l)	92	6	109**	5	>105
MCV (fl)	79·2	5·7	84·4**	4·4	>80·0
MCH (pg)	24·9	2·4	27·0*	2·1	>29·0
HRC (%)	18·5	9·3	14·3	14·2	<2·5
Tfsat (%)	6·2	3·7	32·2**	5·4	>20
Ferritin (μg/l)	7·0	4·0	342·0**	119·0	>15

Hb, Haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular, hemoglobin; HRC hypochromic red cells; Tfsat, transferrin saturation.
Mean values were significantly different from those at day 0 (paired *t* test): *P<0·05, **P<0·01.
† Venofer®; Vifor, St Gallen, Switzerland, 2 × 200 mg/week.
‡ For details of subjects and procedures, see pp. 5–6.

Table 2. Response of haemoglobin, red cell indices, transferrin saturation and ferritin to different doses of parenteral iron–sucrose complex† in postpartum anaemia Iron status in four different studies‡

Total dose (mg iron)…	100 (Study 1)				400 (Study 2)				800 (Study 3)				800 (Study 4)			
	Day 0		Day 14		Day 0		Day 14		Day 0		Day 14		Day 0		Day 14	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hb (g/l)	88	8	111**	7	86	10	115**	10	85	9	114**	9	73	9	105**	9
ΔHb			2·1	0·5			2·8	0·7			2·9	1·1			3·2	0·9
MCV (fl)	85·3	16·2	89·0*	6·0	89·2	6·5	91·0*	7·2	89·4	6·5	91·9**	6·1	90·5	7·2	94·0**	4·7
MCH (pg)	31·3	10·7	29·0	2·0	29·4	2·9	29·8	3·1	29·7	2·5	30·0	2·5	28·5	2·1	29·1**	2·1
HRC (%)	ND		ND		3·3	4·4	5·8	4·9	4·6	4·7	8·1**	7·3	9·4	11·7	16·1**	14·1
Tfsat (%)	15·6	11·9	23·3	8·8	10·4	12·0	17·0	9·0	15·0	12·2	21·8**	10·4	9·7	4·6	22·4**	10·0
Ferritin (μg/l)	30·3	16·8	32·8	10·8	31·9	20·2	81·6**	27·5	47·0	51·0	209·0**	75·0	57·0	47·0	195·0**	89·0

Hb, haemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; HRC, hypochromic red cells; Tfsat, transferrin saturation; ND, not detected.
Mean values were significantly different from those at day 0 (paired *t* test): *P<0·05, **P<0·01.
† Venofer®; Vifor, St Gallen, Switzerland.
‡ For details of subjects and procedures, see pp. 5–6 and Breymann *et al.* (1996, 2000).
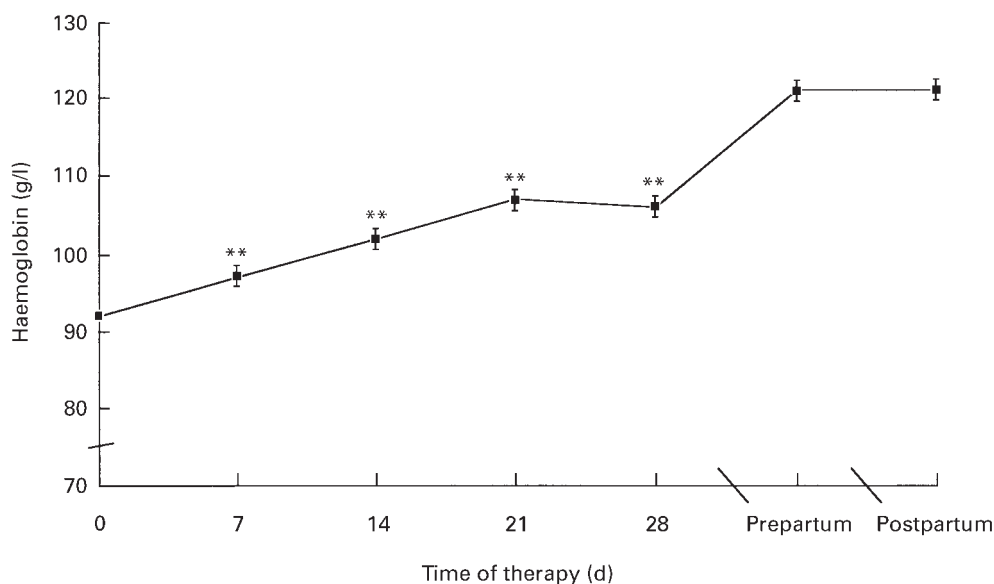
Fig. 1. Reponse of haemoglobin to parenteral iron–sucrose complex (Venofer®; Vifor, St Gallen, Switzerland) in pregnancy anaemia resistant to oral iron therapy (*n* 100). For details of subjects and procedures, see pp. 5–6. Values are means with standard deviations shown by vertical bars. Mean values were significantly different from those at time 0: **P<0·01.

Postpartum

We present the pooled data from four different randomized studies with Fe–sucrose (Venofer®, Vifor) at cumulative doses of 100–800 mg given as a single dose (100 mg, group 1), on 2 d (group 2, 2 × 200 mg), and on 4 d (groups 3 and 4, 4 × 200 mg) (Breymann *et al.* 1996, 2000). Following mean blood loss of 840 (range 300–3600) ml, postpartum Hb ranged from 73 (SD 9) to 88 (SD 0·8) g/l before treatment. Overall response at 14 d (Table 2) showed a dose-dependent increase in Hb (by 21–32 g/l) to normal levels in all groups (Fig. 3); the maximum mean daily increase in group 4 was 0·23 g/l.

In contrast with the pregnancy results, the red cell indices showed clear changes only in mean corpuscular volume; mean corpuscular Hb increased significantly only in group 4. Interestingly, hypochromic red cells increased in all groups, especially group 4 with the
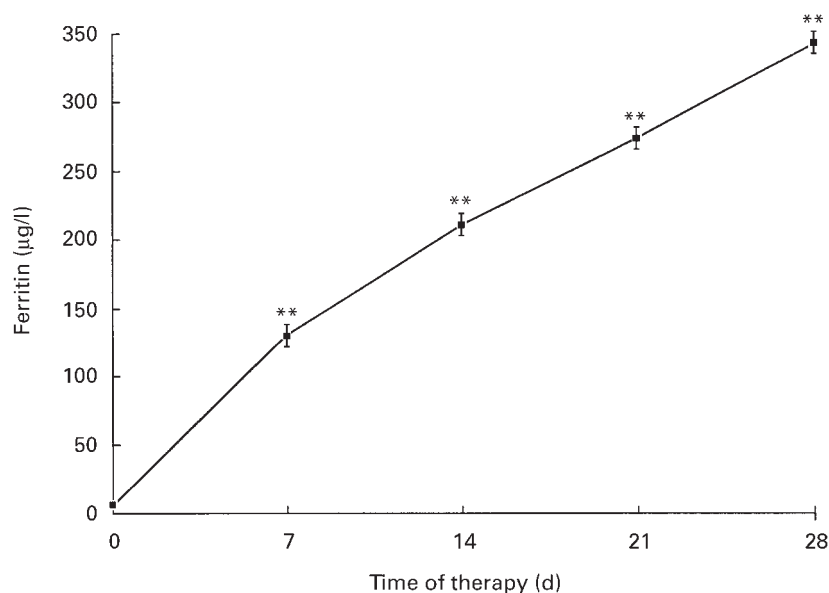

Fig. 2. Response of serum ferritin to parenteral iron–sucrose complex (Venofer®; Vifor, St Gallen, Switzerland) in pregnancy anaemia resistant to oral iron therapy (*n* 100). For details of subjects and procedures, see pp. 5–6. Values are means with standard deviations shown by vertical bars. Mean values were significantly different from those at time 0: **P<0·01.
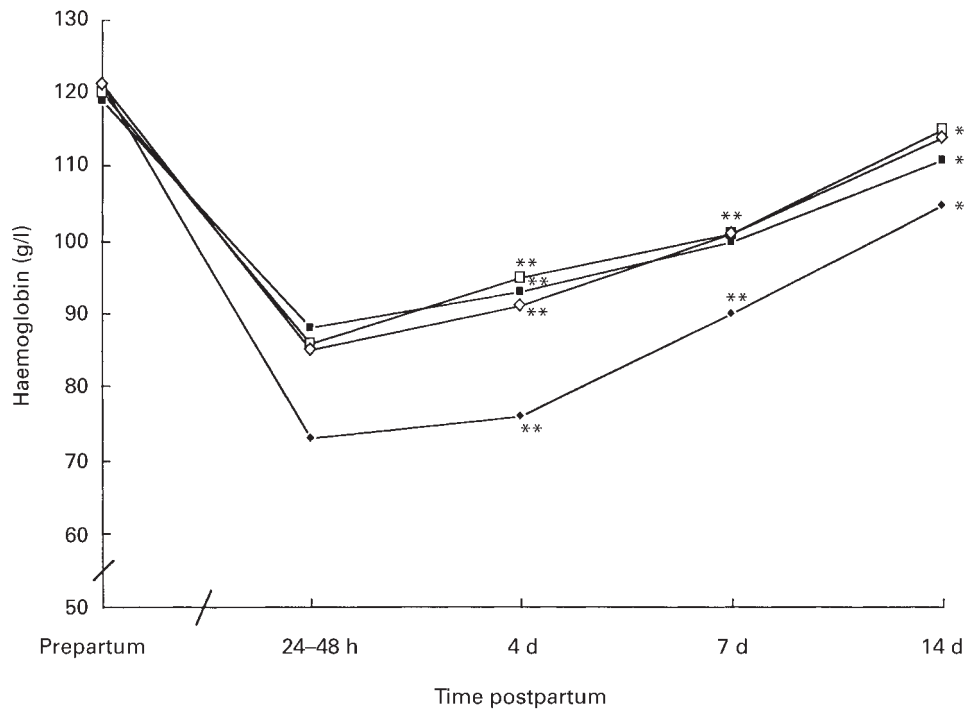
Fig. 3. Response of haemoglobin to parenteral iron–sucrose complex (Venofer®; Vifor, St Gallen, Switzerland) at four different dosage regimens in postpartum anaemia (*n* 400). For details of subjects and procedures, see pp. 5−6 and Breymann *et al.* (1996, 2000). ■, 1 × 100 mg; □ 2 × 200 mg; ◆, 4 × 200 mg; ◇, 4 × 200 mg. Mean values were significantly different from those 24−48 h postpartum; **P<0·01.

lowest initial Hb, suggesting persistent functional Fe deficiency in the presence of forced erythropoiesis. Transferrin saturation and serum ferritin (Fig. 4) increased dose-dependently to high-normal values in all groups.

Discussion

Although Fe is perhaps the most important heavy metal in man, and its absorption and metabolism have been
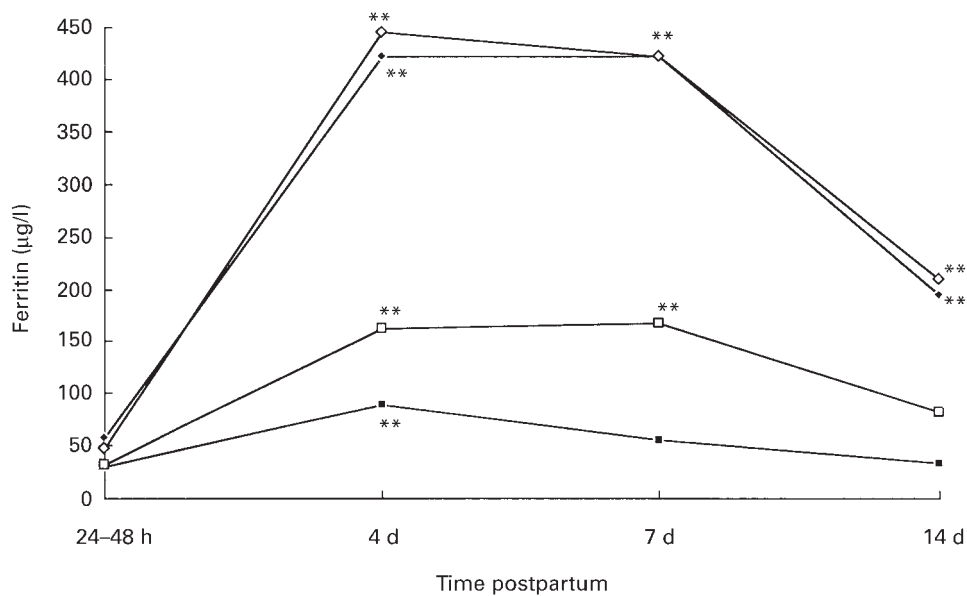

Fig. 4. Response of serum ferritin to parenteral iron–sucrose complex (Venofer®; Vifor, St Gallen, Switzerland) at four different dosage regimens in postpartum anaemia (*n* 400). For details of subjects and procedures, see pp. 5−6 and Breymann *et al.* (1996, 2000). ■, 1 × 100 mg; □, 2 × 200 mg; ◆, 4 × 200 mg; ◇, 4 × 200 mg. Mean values were significantly different from those at 24−48 h postpartum: **P<0·01.

intensively researched for some 40 years, many questions remain unanswered. In particular, the worldwide problem of Fe deficiency has not yet been solved. Despite the complexity of Fe chemistry and the processes of Fe absorption and metabolism, we must continue to strive for an even more detailed understanding of the function of this vitally important metal.

The consequences of Fe deficiency and Fe deficiency anaemia are serious, and include reduced exercise tolerance, stomatitis, gastritis, structural and chemical changes to the hair, nails and skin, and impairment of thermogenesis, thyroid metabolism and catecholamine turnover. Fe-deficiency anaemia during pregnancy may result in low birth-weight and increased preterm birth rate and perinatal mortality. Fe deficiency in the fetus may lead to sometimes irreversible damage to the central nervous system, with impairment of psychomotor development. The prevalence of Fe-deficiency anaemia in different regions of the world ranges from 12 to 43 %.

Increased Fe requirement in pregnancy and the puerperium carries with it an increased susceptibility to Fe deficiency and Fe-deficiency anaemia. Prevention and correction presuppose reliable laboratory variables and a thorough understanding of the mechanisms of Fe therapy. The Hb level alone is insufficient for informing management.

A complete work-up (ferritin, transferrin saturation) is essential, preferably with haematological indices such as hypochromic and microcytic red cells, and reticulocytes, classified by degree of maturity, in particular before parenteral therapy.

Since ferritin acts as both an Fe storage and acute-phase protein, it cannot be used to evaluate Fe status in the presence of inflammation. A high ferritin level thus requires 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 now be used, since it is unaffected by inflammation.

As Fe balance is regulated by gastrointestinal absorption and by Fe lost through cell desquamation in the small intestine (Umbreit et al. 1998), and because free, i.e. non-protein-bound, Fe is potentially toxic, oral Fe administration is normally the treatment of choice. It is effective, safe and cheap, and subject to the natural regulatory mechanism. In exceptional cases, such as inadequate gastrointestinal absorption, poor toleration of the necessary Fe dose, when a rapid effect is required or to avoid blood transfusion, intravenous Fe administration is indicated.

Inadequate understanding of the complex chemistry of parenteral Fe administration was previously responsible for serious side effects, such as toxic and allergic reactions, and even anaphylactic shock, in particular with dextran preparations. This created a somewhat negative attitude to intravenous Fe therapy which persists to this day.

However, the current type II Fe complexes that release Fe to the endogenous Fe-binding proteins with a half-life of about 6 h are not only effective but carry a minimal risk of allergic accident and overload, especially after a comprehensive pretreatment work-up (Macdougall et al. 1989; al-Momem et al. 1996; Danielson et al. 1996; Breymann, 1998; Danielson, 1998; Krafft et al. 2000; Rohling

et al. 2000). Our departmental results over 8 years backed by post-marketing experience in twenty-five countries indicate that Fe–sucrose complex therapy is a valid first-line option for the safe and rapid reversal of Fe-deficiency anaemia.

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