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PROSPECTIVE CLINICAL STUDY ON THE EFFICACY OF LOW DOSES OF IRON FOR PREVENTION OF ANEMIA DURING PREGNANCY IN THE ROUTINE CLINICAL PRACTICE

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Prospective clinical study on the efficacy of low doses of iron for prevention of anemia during pregnancy in the routine clinical practice

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ABSTRACT

Prospective clinical study on the efficacy of low doses of iron for prevention of anemia during pregnancy in the routine clinical practice.

We conducted a prospective not controlled clinical study to evaluate in the routine clinical practice the efficacy of supplementation with iron 40 mg/die during pregnancy in order to prevent anemia. Non smoking, pregnant women, aged 18 years or more, with blood Hb concentration >10 g/dl consecutively observed at their first trimester of pregnancy in the first level outpatient service were eligible for the study. Women were invited to start treatment with a daily iron dose of 40 mg (iron proteinate - Ferplex®, Ferlatum®, Legofer®, Fysiofer®) from 14-18 weeks of gestation (mean 17 weeks) till delivery. The patients were asked to come back for follow up visit and to evaluate Hb and ferritin levels at 24-26 (visit 2) and 34-36 (visit 3) weeks of gestation. A total of 160 women entered the study. The mean blood hemoglobin concentration slightly decreased during pregnancy (entry vs. final visit -1.0±1.0 g/dl). Otherwise, ferritin levels markedly decreased during pregnancy (entry vs. final visit -23.9±29.0 ng/ml). A total of 24/160 women (15%, 95%CI 10.1-23.4) had diagnosis of anemia (Hb concentration was lower than <10.5 g/dl during the second and <11g/dl during the third trimester of pregnancy). The rate of anemic women was 23.5% (16/68) among those with lower ferritin level (≤30 ng/ml) at study entry (p<0.05). Haemoconcentration (Hb greater than 13 g/dl) was observed in 8 (5%) women during the 2nd trimester of pregnancy and in 4 (2.5%) during the third one. Overall 12/160 women (7.5%) reported pirosis, nausea or both. In conclusion the daily supplementation with a complex of 40 mg of iron with succinilate casein is associated with a low incidence of anemia in unselected consecutive pregnant women with an excellent safety profile.

Key words: pregnancy, anaemia, iron deficiency.

SOMMARIO

Studio clinico prospettico sull'efficacia di basse dosi di ferro nella prevenzione dell'anemia gestazionale nella routine clinica.

Abbiamo condotto uno studio prospettico non controllato per valutare, nella pratica clinica quotidiana, l'efficacia di 40 mg/die di ferro per prevenire l'anemia in gravidanza. Sono state reclutate consecutivamente 160 donne gravide, con valori ematici di Hb > 10 g/dl nel primo trimestre. Le donne hanno assunto 40 mg/die di ferro (ferro proteinato - Ferplex®, Ferlatum®, Legofer®, Fysiofer®) dalla 14ª-18ª settimana di gestazione (media 17ª settimana) fino al parto.

La concentrazione media di emoglobina nel sangue si è modestamente ridotta durante la gravidanza (visita basale verso quella finale –1,0±1,0 g/dl). Il livello di ferritina ha mostrato una marcata diminuzione (23,9±29,0 ng/ml): 24/160 donne (15%, 95% CI 10,1 -23,4) hanno sviluppato anemia (concentrazione di Hb <10,5 g/dl nel secondo, <11 g/dl nel terzo trimestre di gravidanza). Nel gruppo di donne con un basso livello di ferritina al reclutamento (≤30 ng/ml) l'incidenza di anemia è stata del 23,5% (16/68; p<0,05).

Emoconcentrazione (Hb >13 g/dl) è stata osservata in 8 (5%) donne durante il secondo trimestre di gravidanza ed in 4 (2,5%) nel terzo. Dodici donne (7,5%) hanno lamentato pirosi, nausea o entrambe. In conclusione, la supplementazione giornaliera con un complesso di 40 mg di ferro e caseina succinilata è associata ad una bassa incidenza di anemia, in un gruppo di donne gravide non selezionate, e ad un ottimo profilo di tollerabilità.

Parole chiave: gravidanza, anemia, carenza di ferro.

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INTRODUCTION

Epidemiological studies have shown that, in the developed countries, about the 2% of women in their fertile age have blood hemoglobin (Hb) levels <10.5 g/dl (1).

Due to the increased iron requirements during pregnancy the global prevalence of anemia among pregnant women is 41.8% (2).

Moderate (between 7 and 9 g/dl Hb) or severe (less than 7 g/dl Hb) anemia in pregnancy is associated with increased risk of maternal and child mortality and infectious diseases (3). Hb levels between 9.5 and 10.5 g/dl during the second trimester of gestation and between 9.5 and 12.5 g/dl at term increase the risk of low birth weight and premature birth (4-6).

Adequate hemoglobin levels in pregnancy have been also shown to lower the risk of neonatal anemia. Thus international organizations have been advocating routine iron for every pregnant woman (7,8).

The suggested dose of iron for prevention of gestational anemia is 60-400 mg die. Higher doses, however, are associated with frequent gastrointestinal symptoms and haemoconcentration.

It has been suggested that 40 mg/die of iron may be enough to prevent anemia in pregnancy (9), thus reducing the frequency and severity of adverse effects. However, clinical studies conducted in the routine clinical practice showing the efficacy of low doses of iron on prevention of anemia in pregnancy are lacking.

Aim of this study was to evaluate the efficacy and the safety of the prevention of anemia with a daily dose of 40 mg of iron in a consecutive population of pregnant women occurring in a first level of outpatient service of a developed country like Italy.

METHODS

This is a prospective not controlled clinical study to evaluate in the routine clinical practice the efficacy of supplementation with iron 40 mg/die during pregnancy in order to prevent anemia. Eligible for the study were non smoking, pregnant women, aged 18 years or more, with blood Hb concentration >10 g/dl consecutively observed at the first trimester of pregnancy in the first level outpatient service of the Unità Operativa Complessa di Ginecologia ed Ostetricia, Azienda Ospedaliera di Desenzano del Garda, during the study period. Exclusion criteria included chronic diseases such as diabetes, chronic hypertension, recurrent abortion, bleeding in pregnancy, any hematological disease (including minor thalassemia). Subjects with contraindications to the use of iron were excluded from the study, according to the contraindications and warnings included in the information sheet of the prescribed product. Vegetarian women were not eligible for the study.

During the entry visit (6-14 weeks of gestation) data about age, weight, medical and obstetric history, current medications were recorded and hemoglobin and ferritin blood levels were tested. Women were invited to start treatment with a daily dose of iron 40 mg (iron proteinate - Ferplex®, Ferlatum®, Legofer®, Fysiofer®) from 14-18 weeks of gestation till delivery. The patients were asked to come back for follow up visit and to evaluate Hb and ferritin levels at 24-26 (visit 2) and 34-36 (visit 3) weeks of gestation. At visit 2 and 3 the woman was questioned toward any potential adverse event related with study drug use.

Data were also collected on the outcome of pregnancy. The protocol did not foresee any specific indication for the management of pregnancy.

Each subject gave written informed consent before interview. The study protocol was approved by the institutional review board of the centre.

The study started on January 2009. The last patients entered the study on September 2009.

Data analysis

Descriptive statistics such as the mean, standard deviation (SD) and proportion were used to describe the characteristics of study subjects. Mean difference between basal and final Hb and ferritin values of each patient were computed.

The 95% confidence interval (CI) of frequencies has been computed according the Poisson's approximation.

According to criteria of U.S. Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), anemia during pregnancy should be diagnosed if a woman's Hb concentration was lower than <10.5 g/dl during the second and <11 g/dl during the third trimester of pregnancy. Iron deficiency was defined has ferritin level <12 ng/ml (10).

RESULTS

Patients characteristics of the 160 women enrolled in the study are reported in Table 1. All included women completed the study. At the entry Hb mean value was 12.7 ± 0.8 g/dl and an iron deficiency (ID) was present in 13/160 (8.1%) women. Women started treatment between the 14 and 18 weeks of gestation (mean 17 weeks).

The blood hemoglobin concentration slightly decreased during pregnancy (entry vs. visit 3: -1.0±1.0 g/dl). Otherwise, ferritin levels markedly decreased during pregnancy (entry vs. visit 3: -23.9±29.0 ng/ml) (Table 2); 24/160 women developed anemia during the pregnancy (Table 3) (15%, 95% CI 10.1-23.4).

The rate of anemic women was 23.5% (16/68) among those with lower ferritin level (≤30 ng/ml) at entry visit ($p<0.05$) (Table 3).

The value of hemoglobin and ferritin at the entry visit were statistically related with the risk to develop anemia during pregnancy. The Odds ratios and 95% CI were respectively 1.96; 1.12-3.43 (p=0.019) and 1.03; 1.01-1.060 (p=0.005).

At the entry visit 55/160 women (34.4%) had Hb value greater than 13 g/dl. Haemoconcentration (Hb >13 g/dl) was observed in 8/160 (5%) and 4/160 (2.5%) women respectively during the second and third trimester of pregnancy. Only in 2 cases Hb values were greater than 13 g/dl during both the 2nd and 3rd trimester. We did not observe any complication for the women or for the foetuses during these pregnancies.

No women interrupted the study treatment for adverse reactions. Overall 12/160 (7.5%) women complied adverse reactions: three

Table 1 - Patients characteristics at the entry visit (n. 160).

Age (years)	Mean ± SD (N) Median (Min - Max)	32.1 ± 4.4 32 (21 - 42)
Weight (kg)	Mean ± SD (N) Median (Min - Max)	59.7 ± 9.4 58 (42 - 91)
Weeks of pregnancy	Mean ± SD (N) Median (Min - Max)	9.7 ± 2.0 9.5 (6 - 14.6)
Hemoglobin (g/dl)	Mean ± SD (N) Median (Min - Max)	12.7 ± 0.8 12.8 (10.2 - 14.7)
Ferritin (ng/ml)	Mean ± SD (N) Median (Min - Max)	43.2 ± 30.0 34.6 (4 - 175)

Table 2 - Changes of hemoglobin (g/dl) and ferritin (ng/ml) during the study period.

	Visit	All Patients (n=160)
Hemoglobin changes vs entry visit		
	Visit 2	
	Mean ± SD (N)	-0.9 ± 0.7
	Median (Min - Max)	-0.9 (-3.2 ; 1.6)
	Visit 3	
	Mean ± SD (N)	-1.0 ± 1.0
	Median (Min - Max)	-0.8 (-4.7 ; 1.2)
Ferritin changes vs entry visit		
	Visit 2	
	Mean ± SD (N)	-21.0 ± 23.1
	Median (Min - Max)	-15 (-106 ; 22.1)
	Visit 3	
	Mean ± SD (N)	-23.9 ± 29.0 (n. 152)
	Median (Min - Max)	-18.6 (-121 ; 43.3)

Table 3 - Rate (%) of anemia in women with ferritin levels >30 ng/ml or ≤30 ng/ml at the entry visit.

Ferritin levels	% (n / N)	Exact two-tailed 95% CI
≤30 ng/ml	23.5 (16/68)	(14.1 - 35.4)
>30 ng/ml	8.7 (8/92)	(3.8 – 16.4)
Total	15.0 (24/160)	(9.8 – 21.5)

women complained pirosis both at 24-26 and 34-36 weeks of gestation (Table 4). At 24-26 weeks of gestation only pirosis was reported in 2.5% women (4/160); at 34-36 weeks of gestation pirosis, nausea and pirosis with nausea were reported respectively 4.4% (7/160), 1.9% (3/160) and 0.6% (1/160) women No other adverse reactions were reported.

Table 4 - Adverse reactions reported during the study. Three women complained pirosis both at 24-26 and 34-36 weeks of gestation.

	Adverse Reaction	% (n / N)
Visit 2	Pirosis	2.5 (4/160)
	No ARs	97.5 (156/160)
Visit 3	Pirosis	4.4 (7/160)
	Nausea	1.9 (3/160)
	Pirosis and Nausea	0.6 (1/160)
	No ARs	93.1 (149/160)

DISCUSSION

A WHO and CDC Technical Consultation on the Assessment of Iron Status at the Population Level has indicated that blood Hb concentration and ferritin are the most efficient indicators for monitoring iron status as a consequence of iron supplementation (11). In this study we have evaluated the changes of these two indicators in an unselected consecutive population of pregnant women supplied with iron.

This study shows that 40 mg/die of iron are useful in prevention of anemia in 85% (136/160) of enrolled women. Fifteen adverse reactions were complained by 12/160 treated women (7.5%). No adverse reactions required the interruption of the study treatment. Haemoconcentration was reported in the five percent of treated women.

Before discussing the results potential limitation should be considered. First of all, this is an uncontrolled study. Further, we have not collected information on diet of study patients, and diet may be relevant for iron intake. However, women were not specifically advised to increase iron intake with diet.

Among the strengths of the study we have to consider the large sample size and the fact that no women was lost to follow up. This study has included a cohort of unselected women consecutively observed to a first level obstetric service, thus giving an estimate of the effect of iron supplementation in routine clinical practice.

In this study the 15% of women had diagnosis of anemia during pregnancy. This proportion is lower than that reported in literature in not supplied women. According to a recent estimate, the global prevalence of anemia among pregnant women is about 40% (2).

In a previous randomized clinical trial conducted in North Carolina (12) 21% of women after the prophylaxis with 30 mg of iron developed anemia. A recent Cochrane review found that the median incidence of anemia in women treated with different daily dose (range 27-200 mg) of iron was 3.5% (range 0-47.2%). With placebo treatment the median incidence of anemia was 32.5% (range 4-85.3%). This results were obtained from 14 randomized controlled clinical trials (13). The incidence of anemia in our unselected consecutive population after prophylaxis with 40 mg of iron was 15%.

Serum ferritin concentration is a marker of iron reserves. Currently, a serum ferritin concentration of less than 12 ng/ml in adults is accepted as an indication of depleted iron stores, even among pregnant women (10). In this study the proportion of women with reduced iron reserve at study entry was 8.1%. This finding confirms the relative high rate of iron deficiency in fertile women even in developed countries and underlines the role of iron supplementation in prevention of anemia in pregnancy.

It is generally accepted that serum ferritin level ≤30 ng/ml indicates an iron reserve of 210-240 mg and the absence of bone marrow haemosiderin (14). In our study the risk of developing anemia was statistically higher in women with serum ferritin level ≤30 ng/ml at study entry (Figure 1), thus identifying a group that should have more benefit by an iron supplementation with a daily dose higher than 40 mg, as already suggested by Milman et al (15).

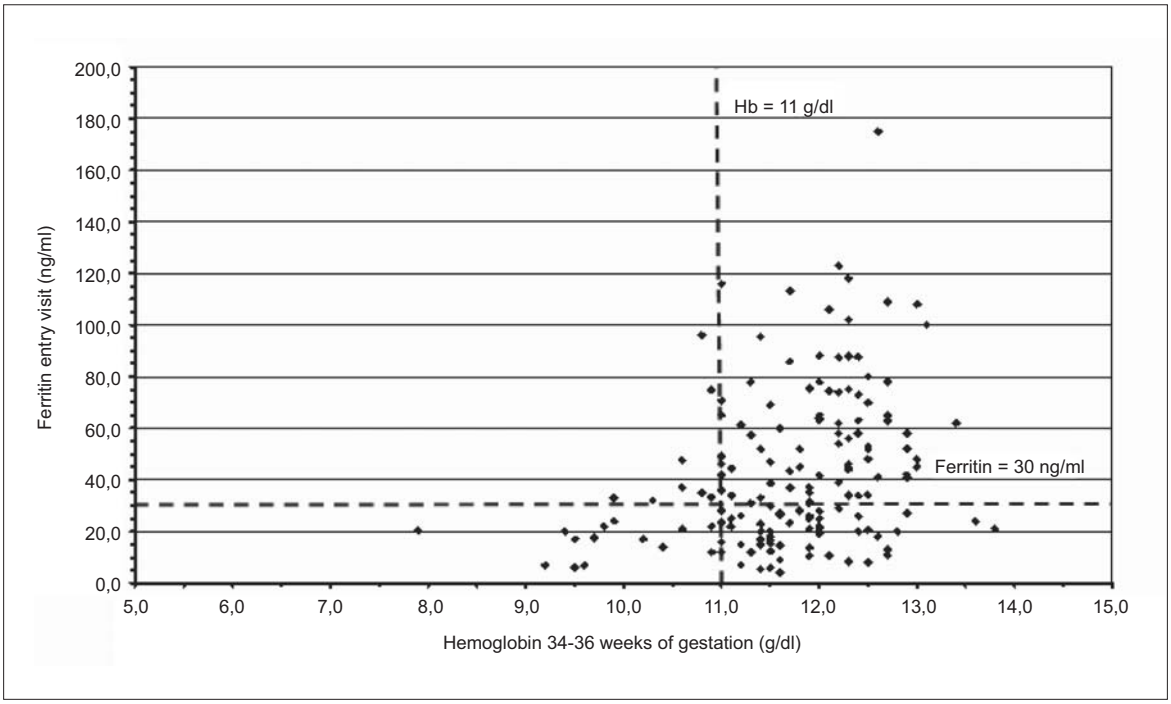

Figure 1. Correlation between value of ferritin at the entry visit and the hemoglobin concentration at 34-36 weeks of gestation.

Iron supplementation in pregnancy, at doses 60 mg to 300 mg of iron/day commonly prescribed by obstetricians in developed countries, may reduce the haemodilution that occur in pregnancy thus causing elevated hemoglobin levels. Haemoconcentration has been associated with plasma volume depletion, pre-eclampsia, eclampsia, pregnancy complications, and low birth weight (1). In this consecutive unselected population 5% of supplied women had Hb level >13g/dl during the second trimester of pregnancy and 2.5% during their third trimester of pregnancy, a proportion lower than that reported in the literature. For example in the large Cochrane review (13) among women who received daily iron supplements, 25% were found to have haemoconcentration (Hb greater than 13 g/dl) at some time during their second or third trimesters, compared with 9% of those who received no iron supplements. It should be underlined that only hemoglobin levels during the third trimester may have consequences on birth weight.

Finally, gastrointestinal adverse reactions including nausea, vomiting and diarrhoea are the most common adverse reactions of iron intake. In the previously quoted Cochrane review data from eight trials involving 3667 women have been pooled (13): the 25% of women who receive daily oral iron supplementation reported adverse reactions of any kind. The rate of reactions was significantly higher in women who received daily higher doses of iron (more than 60 mg).

In this study gastrointestinal adverse effects were reported by 7.5% of women. Not all iron salts have the same safety profile manly with regard to gastroenteric adverse effects. In this study the women were treated with a semi-synthetic iron compound obtained by addition of Fe^{+3} to succinylated casein (iron proteinate - Ferplex®, Ferlatum®, Legofer®, Fysiofer®). In vitro investigations (16) have shown that succinyl carboxyl residues of iron proteinate are highly ionized at neutral – alkaline pH conditions determining high solubility and a potentially good release of iron into the duodenum. Conversely,

iron proteinate remains insoluble at the acidic pH values of the stomach where it precipitates without releasing iron ions. An in vivo study in healthy volunteers has shown results in line with the pre-clinical experience, confirming the tight binding of iron to the succinylated proteins of iron proteinate at acid pH condition (17).

These findings have strong relevance with regards to the gastroenteric tolerability of the product. In particular, the better gastric safety shown by the iron proteinate could be related to the negligible iron release at the acid pH of the stomach.

CONCLUSION

In an unselected consecutive population we confirmed that iron supplementation starting from 14-18 weeks of gestation till delivery is associated with a low incidence of anemia in pregnant women.

The highest rate of anemia was observed in women with lower serum level of ferritin at 6-14 weeks of gestation. This subgroup of patients with serum ferritin ≤30 ng/ml probably needs a daily dose of iron higher than 40 mg.

The use of a complex of ferric salt with succinilate casein may reduce the rate of gastroenteric adverse reactions.

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