Blood ferritin levels in pregnant women as an estimator of low birth weight?

J. Uberos, A. Molina and A. Muñoz

CTS-190 Research Group, 'San Cecilio' University Hospital, University of Granada, Granada, Spain

Key words: **FERRITIN, IRON, LOW BIRTH WEIGHT, GESTATION, PREGNANCY**

ABSTRACT

The aim of this study was to analyze the blood ferritin concentration in pregnant women and to quantify the risk of low birth weight and the impact on growth rates of various blood ferritin levels. The study was carried out in the Obstetrics Department of the Santa Ana Hospital in Motril, Granada, Spain. The sole criterion applied for inclusion in the study was that the gestational age should be between 29 and 34 weeks. In every case, levels of the following were determined: erythrocytes, hemoglobin, hematocrit, glucose, urea, cholesterol, triglycerides, alkaline phosphatase, ferritin, dimer D and fibrinogen. The gestating mothers with low birth weight presented average ferritin levels that were 3.73 ng/ml greater than those observed in women without low birth weight (95% confidence interval (CI): 0.4–7.06 ng/ml). Women with blood ferritin levels greater than 13 ng/ml were 4.5 times more likely to have a small-for-gestational-age baby at 38 weeks of gestation (95% CI: 3.19–5.21). On the basis of our results, we conclude that monitoring the serum ferritin level in maternal blood during gestation and confirming the diminution of ferritin at the appropriate time would provide a useful estimator of normal growth rates and fetal development.

INTRODUCTION

Ferritin is a protein that performs an iron storage function in mammals. It is found mainly in the liver, spleen and bone marrow, and to a lesser extent throughout the tissues. The concentrations of serum ferritin present a close correlation with total reserves of iron in the body; this protein can therefore be used as a reliable estimator of iron reserves in the organism. During gestation, levels of serum ferritin fall by 50%. This is a consequence of the normal heme-iron dilution process during pregnancy, and also of the extraction of iron by the fetus[1]. The utility of ferrotherapy during gestation is still a matter of controversy. Some studies have found beneficial effects for the mother, including a lower rate of anemia[2–4], and for the fetus, where higher levels of ferritin have been found in newborns when the mothers received iron supplements during their pregnancy[5]. Nevertheless, other studies have pointed to the lack of correlation between levels of ferritin in the blood during the second trimester of gestation and the levels at or near birth[6,7]. Furthermore, the rapid extraction of iron from maternal serum by the fetal–placental unit means that the levels of maternal hemoglobin are unreliable indicators of the state of depletion of maternal iron reserves[8].

The aim of this study was to analyze the levels of ferritin in pregnant women and to investigate whether the variability of this biochemical parameter bore any relation to low birth weight. We aimed to estimate the risk of low birth weight and the impact on various indices associated with concentrations of ferritin in the blood.

MATERIALS AND METHODS

The study was carried out between 2 January and 24 May 1996. It included all the pregnant women attending the Obstetrics Department of the Santa Ana Hospital in Motril, Granada, Spain during this period. The sole criterion for inclusion in the study was that

Correspondence: Dr J. Uberos, CTS-190 Research Group, 'San Cecilio' University Hospital, University of Granada, Granada, Spain

ORIGINAL ARTICLE

Received 10–11–99 Accepted 22–3–00

the gestational age should be between 29 and 34 weeks (assigned by last menstrual period). The exclusion criteria were chronic disease affecting the mother (primary or secondary nephropathy, high blood pressure with arteriopathy or nephropathy, ischemic cardiopathy, malignant tumors, chronic anemia) and congenital malformations apparent in the newborn. In calculating sample size, we assumed a low birth weight rate of 10% in our group, adjusted the α error by 0.05 and assumed a β error of 0.2. The goal was to detect a difference of at least 10% in the low birth weight rate between pregnant women presenting the lowest and highest levels of serum ferritin. To meet the above parameters and detect such differences, it was necessary to include at least 250 women in the study.

This project was approved by the Hospital Ethical Committee and consent of parent or guardian was obtained in each case. During the initial interview and before inclusion in the study, the informed consent of the mother was obtained. Subsequently, the following data were obtained: arterial pressure (the average of two readings, with the patient lying down), weight and height. Also, before breakfasting, a blood sample was extracted to determine the erythrocyte count, hemoglobin and hematocrit (using Coulter Electronics apparatus), glucose, urea, cholesterol, triglycerides, alkaline phosphatase (by colorimetric methods), ferritin (by fluorimetric enzyme immunoassay, Baxter Diagnostics), dimer D (Minutex) and fibrinogen (Electra 1000 Coagulometer, Baxter Diagnostics). All the women presenting hemoglobin below 11 g/dl were given ferrous sulfate (40 mg/day) from week 20 of gestation. After the birth, somatometry data were obtained in the newborn.

For the statistical analysis, we used the Kolmogorov normality test, *t* test, Pearson correlation study, study of linear and logistic regression, survival analysis (Kaplan–Meier and actuarial) and regression analysis of proportional risks (Cox).

RESULTS

Of the 226 pregnant women included in the study, 19 (8.4%) presented low birth weight and 201 (88.9%) had a baby with normal birth weight for gestational age; we used the fetal growth tables of our country (Andalucia, Spain). Contact was lost with four subjects (2.7%) during the course of the study and two newborns were excluded, as they presented malformations – congenital hydronephrosis and harelip, respectively.

Anemia (hemoglobin < 11 g/dl) was observed in 29.9% of the women presenting normal uterine growth rates and in 5.6% of those presenting low birth weight ($\chi^2 = 4.86$; $p = 0.02$). Other factors traditionally held to influence the development of uterine growth, such as maternal age, parity or tobacco smoking, did not differ to a significant extent between the two groups in our sample (Table 1). The blood ferritin did not differ significantly between the smokers and the non-smokers. In the women with low birth weight, ferritin levels were 3.95 ng/ml higher than in those without low birth weight (95% CI 0.63–7.29 ng/ml). We recalculated the power of our study ($1 - \beta$) and found a 65.2% probability that these differences would be detected for an α error of 0.05%. A regression analysis between the maternal hematocrit and blood ferritin level revealed a value of $F = 3.69$ ($p = 0.056$) for the analysis of variance.

One of the main problems confronting this study was that, although all the women were included at approximately 31 weeks of gestation (95% CI 31.3–31.6), the exact birth date was unpredictable and each woman was included in the study for different periods of time. Two groups of pregnant women were considered: those having blood ferritin levels of ≥ 13 ng/ml (the upper limit in the 95% CI for ferritin in pregnant women without low birth weight) or those with lower levels. Cumulative rates for low birth weight in the women with ferritin levels of 13 ng/ml or above were found to be lower than those in women with lower ferritin levels. Significant differences were found when we compared the curves of the two groups of women ($\chi^2 = 5.36$; $p < 0.02$) (Figure 1). Stratification of the data taking tobacco consumption into account revealed significant differences for non-smokers (Figure 2) between the curves of the women with blood ferritin levels of ≥ 13 ng/ml ($\chi^2 = 7.22$; $p < 0.007$). However, for the smokers, the two curves overlapped (Figure 3) ($\chi^2 = 0.30$; $p < 0.58$). This fact lends further weight to the hypothesis that tobacco consumption is an effect-modifying variable in the relationship under study (between blood ferritin in the pregnant woman and birth weight).

Table 1 Mean (SD) of the variables studied in pregnant women with and without low birth weight

	Controls	Low birth weight	Significance
Mother's age (years)	28.2 (5.3)	26.1 (5 9)	NS
	95% CI 27.4–28.9	95% CI 22.7–28.2	
Erythrocytes (10^6/ml)	3.90 (0.33)	4.13 (0.25)	***
	95% CI 3.85–3.95	95% CI 4.01–4.26	
Hemoglobin (g/dl)	11.4 (0.88)	12.3 (1.04)	***
	95% CI 11.3–11.5	95% CI 11.8–12.8	
Hematocrit (%)	34.4 (2.4)	36.8 (2.5)	***
	95% CI 34.1–34.8	95% CI 35.1–38.1	
Alkaline phosphatase (UI)	235.6 (68.1)	302.5 (79.5)	***
	95% CI 225.6–245.6	95% CI 263.0–342.1)	
Ferritin (ng/ml)	12.2 (6.3)	15.9 (7.9)	**
	95% CI 11.3–13.1	95% CI 11.7–20.1	
Systolic arterial pressure (mmHg)	107.4 (12.3)	110.9 (13.4)	NS
	95% CI 105.8–109.6	95% CI 104.2–117.6	
Diastolic arterial pressure (mmHg)	66.1 (7.3)	68.8 (9.9)	NS
	95% CI 65.2–67.3	95% CI 63.9–73.8	
Glucemia (mg/dl)	83.5 (6.8)	81.7 (6.4)	NS
	95% CI 82.5–84.6	95% CI 78 5–84.9	
Dimer D (> 250 µg/ml)	39/154	8/16	*
Fibrinogen (mg/dl)	543.4 (101.6)	545.6 (133.9)	NS
	95% CI 528.5–558.3)	95% CI 479–612.2	

* $p < 0.05$; ** $p = 0.02$; *** $p < 0.05$; NS, not significant

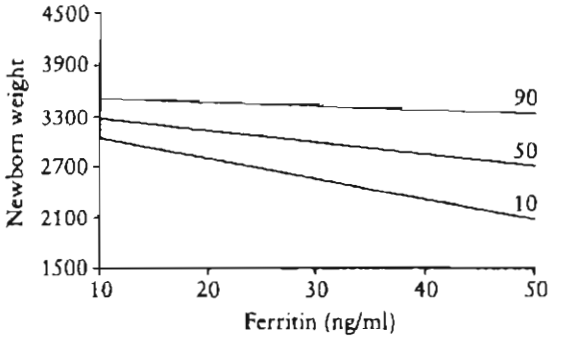

Figure 1 Simple linear regression between newborn birth weight and maternal blood ferritin levels. The 10th, 50th and 90th centiles are shown

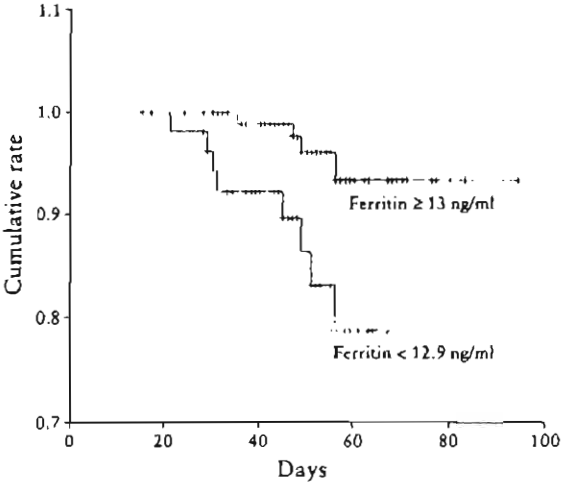

Figure 2 Cumulative analysis of low birth weight for non-smoking pregnant women presenting serum ferritin levels of ≥ 13 ng/ml and of < 12 9 ng/ml

On evaluating the hazard rate, which in our study represented the day-to-day probability of each woman having a low birth weight, we found that approximately 28 days after being included in the study, the higher the concentration of ferritin in the blood, the higher the hazard rate presented by the women.

Women with blood ferritin levels greater than 13 ng/ml were 4.5 times more likely to have a