Iron but not folic acid supplementation reduces the risk of low birthweight in pregnant women without anaemia: a case–control study

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ABSTRACT

Objective: To assess whether iron and folic acid supplementation reduce the risk of low birthweight (LBW) in women without anaemia.

Design: Case–control study.

Setting: University Hospital of Cantabria.

Study population: Cases were 322 mothers without anaemia delivering a singleton infant of less than 2500 g. Controls were 934 mothers without anaemia delivering a term non-small-for-gestational-age infant.

Data collection: Data on iron and folic acid supplementation were obtained from prenatal chart record and personal interview. Data on risk factors for LBW were also gathered.

Results: Agreement between the two sources of information was good (82% for folic acid and 94% for iron). Odds ratios yielded from the two sources were very close. Folic acid only (15 mg/day) was unrelated to LBW, whereas iron supplementation (80 mg ferrous sulphate) was associated with a lower risk of LBW (odds ratio (OR) 0.58, 95% CI 0.34 to 0.98), adjusted for smoking, maternal education, body mass index, obstetric diseases during pregnancy, weight gain during pregnancy, and previous LBW. The results of iron plus folic acid were similar to those for iron (OR 0.56, 95% CI 0.33 to 0.96). There was a significant trend towards a lower risk of LBW ($p<0.001$) with the duration of iron supplementation. After stratifying by the type of LBW, the trend was also significant for any kind of LBW.

Conclusions: Iron supplementation is associated with a lower risk of LBW in pregnant women without anaemia.

Current knowledge indicates that anaemia in pregnancy is a risk factor for preterm delivery and subsequent low birthweight (LBW).[1 2] The US Preventive Services Task Force in 1996 concluded that there was currently insufficient evidence to recommend for or against the routine use of iron supplements for healthy pregnant women,[3] and this statement has not changed since then.[4] Nevertheless, routine iron and folic acid supplementation is recommended during pregnancy to avoid the deleterious effect of anaemia on birthweight.[2 5] Not all women in developed countries receive iron supplementation.[5–8] It has been suggested that a selective supplementation reserved for women with anaemia should be preferred to routine supplementation because iron is a potentially toxic element and unjustified supplementation could expose women to high levels of iron and to oxidative stress, which is also observed in pregnancy pathologies (preeclampsia, gestational diabetes).[9]

Two clinical trials in pregnant women without anaemia in developed countries have been reported. The first was performed on 275 low-income women from Cleveland, Ohio, United States, for whom data on birthweight were available for 213 women; the study reported a fourfold lower incidence of LBW (from 17% to 4%) in the treatment arm, 30 mg iron for approximately 10 weeks.[10] The second trial, reported in 2006, randomly assigned US women eligible for the Special Supplemental Nutrition Program for Women, Infants and Children, into four arms in 1997–1999.[11] Two arms were women without anaemia, 218 were assigned to receive iron (30 mg) and 211 were assigned to placebo. Data were reported on the outcomes of 166 and 168 women of the treatment and placebo arms, respectively. The frequency of several outcomes in the treatment and placebo groups were as follows: LBW 4.8% versus 9.5% ($p = 0.09$); small for gestational age (SGA) 10.8 versus 15.5% ($p = 0.22$); and preterm delivery 7.5% versus 13.9 ($p = 0.05$). Despite these results, there are doubts about the benefits of iron supplementation and therefore it is not fully endorsed.[12 13] Currently available evidence is thus insufficient to support or reject this practice for the specific purposes of raising birthweight.[14]

Observational studies provide a lower evidence level than trials, although they can be useful in evaluating programmes in the field. We present the results of a case–control study to assess whether iron and folic supplementation among pregnant women without anaemia is associated with LBW.

METHODS

The study population includes women seen at the University of Cantabria Hospital (Spain), a non-profit 1200-bed referral centre serving 525 000 people (the entire region of Cantabria, northern Spain). Case and control groups were collected from 1 April 1998 to 30 November 2002. The Ethics Committee of the hospital authorised the study. Oral informed consent was sought from every eligible woman.

Eligibility criteria for cases were the delivery of a single live infant weighing less than 2500 g without congenital malformations during the study period, residence in the referral area of the hospital, receiving prenatal care (first visit in the first trimester and at least five visits during pregnancy), and without anaemia during pregnancy (anaemia was defined as a haemoglobin level less than 11 g/l regardless of gestational age). No woman declined

Table 1 Description of the study population according to sociodemographic characteristics (age, education, primiparity), characteristics of the infant (weight, gestational age) and risk factors for low birthweight (smoking, body mass index, weight gain per week during pregnancy)

Variable	Cases (n = 322)	Controls (n = 934)	p
Maternal age, years, %			
⩽20	4.0	4.1	
21–35	81.4	85.3	
>35	14.6	10.6	0.154
Maternal education, %			
⩽ Primary school	20.5	23.2	
Secondary	71.7	66.0	
University	7.8	10.8	0.122
Primigravidae, %	48.5	45.5	0.361
Smoking in pregnancy, %			
No	56.5	67.0	
1–10 cigarettes/day	33.5	27.6	
>10 cigarettes/day	10.0	5.4	<0.001
Body mass index (SEM), kg/m^2	23.2 (0.2)	23.7 (0.1)	0.031
Weight gain per week during pregnancy (SEM), g	255 (6)	296 (3)	<0.001
Weight of infant (SEM), g	2041 (25)	3340 (14)	<0.001
Gestational age (SEM), days	250 (1)	277 (1)	<0.001

to participate. A total of 322 cases were included; 187 were preterm and 108 were SGA.

The selection of controls was as follows. A random sample of one sixth of all women delivering at the hospital was drawn by using the following procedure: each month for the study period, all women delivering on five days, randomly selected in advance, were asked to participate (n = 1550). Forty-nine women had already been identified and included in the group of cases or they had a preterm or SGA infant, 11 women had infants with congenital malformations, 28 women declined participation, 528 did not receive adequate prenatal care (as defined for cases) and information on anaemia status was lacking, leaving 934 women in the control group.

Three sources of data were used: personal interviews (carried out within the three days after delivery), clinical charts, and prenatal care records. Information was obtained on the following variables: mother's vital data (age at pregnancy, race, education level, marital status, socioeconomic class, and occupation, from interview), obstetric history (parity and abortions, from the prenatal care record), previous adverse perinatal outcomes, conditions during pregnancy (infections, preeclampsia, diabetes, and other obstetric conditions from the prenatal care record), birthweight (weight in grams in the delivery room), prescribed and over-the-counter drugs (from both prenatal care record and from interview), smoking during pregnancy (interview), and prenatal care (number of visits and date of first visit, from prenatal care record and interview in those receiving private care). Social class was coded in five main levels (ranging from I, the highest, to V, the lowest) according to the classification of the Spanish Society of Epidemiology,[15] which is close to that of the Black Report.[16] Information on iron and folic supplementation and other supplements was obtained from two sources: personal interview and prenatal care record. Data on the duration of intake were obtained by personal interview (this information was not included in the prenatal care record) after asking for the date of pregnancy when intake began and the date of pregnancy when medication was stopped. A woman was included in the group "taking supplements" if the duration of intake lasted at least one week.

Comparison of proportions was assessed by the Fisher's exact test and the *t*-test was applied to compare means. The

Table 2 Association between folic acid, iron supplementation and risk of low birthweight using two sources of information (prenatal care record and maternal interview)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR* (95% CI)
From prenatal care record				
No.	24	44	1 (ref.)	1 (ref.)
Folic acid only	11	16	1.26 (0.45 to 3.44)	1.31 (0.50 to 3.42)
Iron only	82	248	0.61 (0.34 to 1.11)	0.59 (0.33 to 1.07)
Folic acid plus iron	120	365	0.60 (0.34 to 1.08)	0.55 (0.31 to 0.96)
NA	85	261		
From maternal interview				
No.	27	54	1 (ref.)	1 (ref.)
Folic acid only	14	17	1.65 (0.64 to 4.16)	1.43 (0.59 to 3.47)
Iron only	145	452	0.64 (0.38 to 1.10)	0.58 (0.34 to 0.98)
Folic acid plus iron	134	407	0.66 (0.39 to 1.13)	0.56 (0.33 to 0.96)
NA	2	4		

NA, Not available; OR, odds ratio.
Crude and multiple risk factor-adjusted for (logistic regression) analyses.
*Adjusted for smoking, maternal education, maternal age, Kessner index, body mass index, obstetric diseases during pregnancy, gestational age, and weight gain during pregnancy.

Table 3 Duration of folic acid and iron supplementation and risk of low birthweight using the information from maternal interview

	Cases	Controls	Crude OR (95% CI)	Adjusted OR* (95% CI)
Folic acid (days)				
⩽60	90	252	1.05 (0.77 to 1.43)	0.98 (0.72 to 1.34)
61–120	41	104	1.16 (0.76 to 1.76)	1.01 (0.66 to 1.54)
>150	17	66	0.76 (0.41 to 1.35)	0.79 (0.44 to 1.42)
p for trend			0.569	0.474
Iron (days)				
⩽60	85	141	1.04 (0.64 to 1.72)	0.96 (0.58 to 1.59)
61–120	95	265	0.62 (0.39 to 1.00)	0.54 (0.34 to 0.88)
>120	99	450	0.38 (0.24 to 0.61)	0.35 (0.22 to 0.56)
p for trend			<0.001	<0.001

NA, Not available; OR, odds ratio.
Crude and multiple risk factor-adjusted for (logistic regression) analyses.
*Adjusted for smoking, maternal education, maternal age, Kessner index, body mass index, obstetric diseases during pregnancy, gestational age, and weight gain during pregnancy.

agreement between the data provided by the two sources of iron and folic supplementation was assessed by the kappa statistic. Associations between the supplements (from the two sources) and LBW were assessed by odds ratio (OR) and its 95% confidence interval (CI). Multiple risk factor-adjusted OR were estimated by means of logistic regression. To determine variables to be included in multivariate logistic regression analysis, the procedure described by Sun *et al.*[17] was followed. Intermediate variables were discarded. Two stepwise models were run, one backward and another forward, allowing the entry of variables with $p<0.2$.[18 19] We made a list of predictors of LBW identified in other studies. With information from stepwise models and the list of predictors, a saturated model was built, and by using a heuristic approach, variables that did not change the coefficient of birthweight by more than 10% were discarded.[18] The objective was to have a parsimonious model retaining all important confounders. All analyses were repeated, stratifying by gestational age (preterm and term LBW) and SGA (yes/no). If substantial differences were found, they are mentioned as footnotes in tables and noted in the text. The Stata 8.0-SE statistical package (Stata Corp., College Station, Texas, USA) was used in analyses.

RESULTS

Characteristics of the study population are listed in table 1. Cases and controls do not differ significantly with regard to maternal age and education. Smoking was more frequent in cases. Controls had a higher body mass index and weight gain during pregnancy. Agreement between the information from personal interview and prenatal care record was high, 82.1% for folic acid and 93.6% for iron. Kappa statistics were 0.64 (SEM 0.03) for folic acid and 0.55 (SEM 0.03) for iron supplementation.

All women reporting folic acid supplementation took one of the following two drugs (single supplement): pills of folic acid 5 mg/three times a day or one pill a day of folinic acid 15 mg. Some 91.8% (256/279) of the cases and 93.0% (799/859) of controls taking iron supplementation took one pill a day (single supplement) of ferrous sulphate 80 mg.

As folic acid and iron are commonly used simultaneously, the independent association of each supplementation was assessed separately (table 2). The results with both sources of information, interview and prenatal care chart, were similar. Women taking folic acid only did not show any relationship with LBW. The strength of the association between iron only and LBW was similar to that obtained with folic acid plus iron (very close OR) and approximately halved the risk of LBW.

The relationship between the duration of use of the supplements and the risk of LBW is shown in table 3. Folic acid was unrelated to the risk of LBW. Stratified analyses by type of LBW (either preterm or term, SGA or non-SGA) gave similar results (data not shown). There was also a decreasing trend of LBW risk with the increasing length of iron supplementation ($p<0.001$). This trend was also statistically significant for all categories of LBW; a duration longer than four months of supplementation gave significant protective OR for term LBW (OR 0.40, 95% CI 0.20 to 0.81), preterm LBW (OR 0.27, 95% CI 0.15 to 0.49), SGA (OR 0.43, 95% CI 0.20 to 0.90) and non-SGA (OR 0.31, 95% CI 0.18 to 0.53).

Finally, we assessed whether iron supplementation was associated with preeclampsia and gestational diabetes (table 4).

Table 4 Association of iron supplementation with preeclampsia and gestational diabetes in both groups (cases and controls) separately

	Controls			Cases		
	Iron supplementation			Iron supplementation		
Condition	Yes n (%)	No n (%)	p Value	Yes n (%)	No n (%)	p Value
Preeclampsia						
Yes	29 (3.4)	7 (9.9)	0.016	48 (17.2)	14 (34.2)	0.018
No	830 (96.6)	64 (90.1)		231 (82.8)	27 (65.9)	
Gestational diabetes						
Yes	36 (4.2)	5 (7.0)	0.233	17 (6.1)	3 (7.3)	0.730
No	823 (95.8)	66 (93.0)		262 (93.9)	38 (92.7)	

Information was missed in two cases and four controls.

As this is a case–control study, associations were ascertained in cases and controls separately. No difference was found in gestational diabetes; the frequency was similar with and without iron supplementation in both cases and controls. Preeclampsia was, however, significantly less frequent in women taking iron supplementation in both cases and controls.

DISCUSSION

Our results suggest that iron but not folic acid supplementation in women without anaemia is associated with a lower risk of LBW without increasing other adverse conditions. These results come from an observational study and they may suffer from a higher likelihood of bias than clinical trials. A potential drawback is recall bias. It is unlikely that this bias could explain our results as information from prenatal maternal chart yielded similar results to that from maternal interview. One advantage of observational studies is that they provide data on the effectiveness of an intervention under actual conditions.

The benefits of iron supplementation in pregnant women have been studied in several trials. In three trials iron supplementation was compared with placebo and no distinction between anaemia and non-anaemia during pregnancy was made. In an Indian trial, it reduced the incidence of LBW,[20] whereas in an American trial it increased birthweight and reduced preterm delivery but not SGA.[11] In a third trial in Wisconsin (USA) on women with prepregnancy normal iron stores, however, no significant differences were seen in maternal or neonatal health, although the number of women was small.[21]

Concerns have been raised about the potential disadvantages of giving iron supplementation to women without anaemia.[8] There have been two American trials on low-income women without anaemia. In the Cleveland trial women receiving a dose of 30 mg per day had a fourfold reduction (from 17% to 4%) in the risk of LBW, mainly preterm LBW;[10] however, the study was not powered to detect any influence on SGA. In the Raleigh trial,[11] the risk of LBW in the treatment group was halved, although the figure was not significant ($p = 0.09$). These results agree with ours. There is also evidence from a case–control study on all pregnant women (with and without anaemia) that iron supplementation prevents SGA.[22]

Regarding the association between folic acid and birthweight, a systematic review published in 1997,[23] combining five trials (with 447 treated women versus 438 placebo), suggested that folic acid decreases term LBW (OR 0.60, 95% CI 0.37 to 0.97); most of the trials included in the review defined their populations poorly, did not give details of randomisation procedures, and did not take iron supplementation into account, although it was routine. It has been found that serum folate concentrations showed negative relationships with the incidence of foetal growth retardation as well as the birthweight of infants,[24–26] although a previous study had shown that anaemia other than iron deficiency was unrelated to LBW and preterm delivery.[1] In New Zealand, a case–control study of SGA folic acid supplementation also showed a reduced risk.[22] In a Danish trial the effects of supplementing the diet with folic acid given preconceptionally or in the first half of pregnancy were a slight increase of birthweight and a decrease in the incidence of preterm labour, LBW and SGA; the greatest effect was seen in the groups receiving folic acid preconceptionally.[27] Other trials have, however, failed to show any advantage of folic acid supplementation on birthweight.[28 29]

We have not reported the effect of supplementing other micronutrients on LBW. The number of women using these supplements was small (16 cases and 66 controls). The available trials have reported conflicting results. Two trials carried out in developing countries and comparing multiple micronutrient supplementation with folic acid plus iron have shown a decreased LBW in women with anaemia only[30] and an increase in birthweight.[31] Another trial showed a slight beneficial effect, although the results did not achieve statistical significance.[32] Finally, another trial on semirural women in Mexico did not report a greater advantage over iron-only supplementation.[33] A Cochrane review found that multiple micronutrient supplementations were not better than folic acid plus iron supplements.[34]

Our results suggest that iron but not folic acid supplementation in women without anaemia is associated with a lower risk of LBW. The main goal of iron supplementation is to avoid iron deficiency, which could cause LBW by several mechanisms.[35] There is, however, a danger of adverse effects if iron is supplemented above the needs of pregnancy.[8] Much of the information on the benefits of supplementation come from studies carried out in developing countries where malnutrition is common. Two trials on women without anaemia have recently been reported in the developed world showing the benefits of iron supplementation, one with data on 213 women[10] and the other on 334 women[11]. Observational studies, such as ours, can provide useful information while waiting for a larger trial with enough statistical power to detect all the benefits and adverse effects in women without anaemia.

What this paper adds

Iron supplementation is associated with a lower risk of LBW in pregnant women without anaemia without increasing preeclampsia or gestational diabetes

Policy implications

The results suggest that a small-dose iron supplementation should be recommended to all pregnant women

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