

Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial¹⁻³

Maria Makrides, Caroline A Crowther, Robert A Gibson, Rosalind S Gibson, and C Murray Skeaff

ABSTRACT

Background: Iron deficiency anemia (IDA) is common in pregnant women, but previous trials aimed at preventing IDA used high-dose iron supplements that are known to cause gastrointestinal side effects.

Objective: The objective was to assess the effect on maternal IDA and iron deficiency (ID, without anemia) of supplementing pregnant women with a low dosage (20 mg/d) of iron. Effects on iron status were assessed at the time of delivery and at 6 mo postpartum. Gastrointestinal side effects were assessed at 24 and 36 wk of gestation.

Design: This was a randomized, double-blind, placebo-controlled trial of a 20-mg daily iron supplement (ferrous sulfate) given from 20 wk of gestation until delivery.

Results: A total of 430 women were enrolled, and 386 (89.7%) completed the follow-up to 6 mo postpartum. At delivery, fewer women from the iron-supplemented group than from the placebo group had IDA [6/198, or 3%, compared with 20/185, or 11%; relative risk (RR): 0.28; 95% CI: 0.12, 0.68; $P < 0.005$], and fewer women from the iron-supplemented group had ID (65/186, or 35%, compared with 102/176, or 58%; RR: 0.60; 95% CI: 0.48, 0.76; $P < 0.001$). There was no significant difference in gastrointestinal side effects between groups. At 6 mo postpartum, fewer women from the iron-supplemented group had ID (31/190, or 16%, compared with 51/177, or 29%; RR: 0.57; 95% CI: 0.38, 0.84; $P < 0.005$). The rate of IDA between the groups did not differ significantly at 6 mo postpartum.

Conclusion: Supplementing the diet of women with 20 mg Fe/d from week 20 of pregnancy until delivery is an effective strategy for preventing IDA and ID without side effects. *Am J Clin Nutr* 2003;78:145-53.

KEY WORDS Iron, pregnancy, iron deficiency, randomized controlled trial

INTRODUCTION

Pregnant women can be at risk of developing iron deficiency (ID) because of the extra iron required by the growing fetus, the placenta, and the increased maternal red cell mass (1, 2). The exact prevalence of ID without anemia and of iron deficiency anemia (IDA) during pregnancy in women in industrialized countries is not well documented but is thought to be high on the basis of pregnancy surveillance data (3) and the results of randomized trials (4).

IDA is characterized by impaired heme synthesis and hypoplastic erythropoiesis (5). In industrialized countries, the postulated risks

of IDA to pregnant women are increased fatigue and decreased work performance, cardiovascular stress due to inadequate hemoglobin and low oxygen saturation, impaired resistance to infection, and poor tolerance to heavy blood loss and surgical interventions at

¹ From the Child Nutrition Research Centre, Child Health Research Institute, and Department of Paediatrics, University of Adelaide, Women's & Children's Hospital, North Adelaide, Australia (MM); the Maternal Perinatal Clinical Trials Unit, Department of Obstetrics & Gynaecology, University of Adelaide, Women's & Children's Hospital, North Adelaide, Australia (MM and CAC); the Child Nutrition Research Centre, Child Health Research Institute and Department of Paediatrics & Child Health, Flinders Medical Centre, Bedford Park, Australia (RAG); and the Department of Human Nutrition, University of Otago, Dunedin, New Zealand (RSG and CMS).

² Supported by the Channel 7 Children's Medical Research Foundation, the Women's & Children's Hospital Perinatal Pathology Fund, the Gunn & Gunn Medical Research Foundation, and Soul Pattinson Manufacturing. MM was supported by a National Health & Medical Research Council Applied Health Sciences Fellowship and a National Health & Medical Research Council R Douglas Wright Fellowship. The iron and placebo tablets were manufactured and donated by Soul Pattinson Manufacturing, Kingsgrove, New South Wales, Australia.

³ Reprints not available. Address correspondence to M Makrides, Child Nutrition Research Centre, Level 1, Clarence Rieger Building, Women's & Children's Hospital, 72 King William Road, North Adelaide SA 5006, Australia. E-mail: makridesm@mail.wch.sa.gov.au.

Received September 4, 2002.

Accepted for publication December 23, 2002.

TABLE 1Definitions of iron status for women during pregnancy and the postpartum period¹

| | Iron sufficiency | Iron deficiency without anemia | Iron deficiency anemia |
|------------------------------|--|---|--|
| Pregnancy: 20 wk to delivery | Hb \geq 110 g/L and ferritin \geq 12 μ g/L | Hb \geq 110 g/L and ferritin $<$ 12 μ g/L | Hb $<$ 110 g/L and ferritin $<$ 12 μ g/L |
| Postpartum: 6 mo | Hb \geq 120 g/L and ferritin \geq 15 μ g/L | Hb \geq 120 g/L and ferritin $<$ 15 μ g/L | Hb $<$ 120 g/L and ferritin $<$ 15 μ g/L |

¹The more conservative cutoffs reflect the physiologic hemodilution that occurs in pregnancy. Hb, hemoglobin. From reference 16.

30–60 mg Fe/d (6). Despite these practices, we could find no published randomized trial that assessed the benefits and risks of low-dose iron supplementation during pregnancy.

The Australian recommended dietary intake (RDI) for iron during pregnancy is 22–36 mg/d, compared with 12–16 mg/d for non-pregnant women, and these recommendations are not dissimilar to those of other industrialized countries (12). Given that the average iron intake of Australian pregnant women is estimated to be 12 mg/d (13), we designed a trial to assess the effect of iron supplementation at a level (20 mg/d) that would ensure that most women in the intervention group at least met the RDI. Primary outcomes were the incidence of maternal IDA at delivery, maternal iron status at 6 mo postpartum, and gastrointestinal side effects at 24 and 36 wk of gestation. Secondary outcomes were the proportion of women requiring high-dose iron treatment during pregnancy, maternal indexes of well-being as measured by a self-administered questionnaire at 36 wk of gestation and at 6 wk and 6 mo postpartum (14), and maternal serum zinc status at delivery and at 6 mo postpartum.

SUBJECTS AND METHODS

Participants

Eligible women attending antenatal clinics at the Women's & Children's Hospital, Adelaide, were enrolled according to the protocol approved by the Research Ethics Committee. Eligible women had singleton or twin pregnancies. Women were excluded if they had preexisting anemia (defined as a hemoglobin concentration $<$ 110 g/L), had thalassemia, had a history of drug or alcohol abuse, or were taking vitamin and mineral preparations containing iron. After obtaining informed consent, we collected baseline sociodemographic information such as age, parity, race, smoking habits, level of education, and usual occupation for the women and their partners (15).

Randomization and blinding

A computer-generated randomization schedule, with balanced blocks and stratified for parity (first pregnancy to reach 20 wk of gestation or second or subsequent pregnancy to reach 20 wk of gestation), was generated by an independent consultant. Opaque bottles with childproof lids were marked with a sequential, numerical code and were filled according to the randomization schedule by the Pharmacy Department at Women's & Children's Hospital. Trial participants and the research team were unaware of the group assignment. At 6 wk postpartum, the women were asked to guess their assigned treatment group. The trial was unblinded after the analysis of primary outcomes.

Treatments

Active supplements were ferrous sulfate tablets, each containing 20 mg elemental iron. Placebo tablets, which were identical in color, size, and shape, contained only excipients. Both the iron and the placebo tablets were manufactured and donated by Soul

Pattinson Manufacturing, Kingsgrove, New South Wales, Australia. Soul Pattinson Manufacturing had no involvement in the design or conduct of the study or in the analysis or interpretation of the data.

Women were asked to take one tablet daily between meals (2) from week 20 of gestation until delivery. Monthly telephone calls (at 24, 28, 32, 36, and 40 wk of gestation) were made to encourage compliance and assess the average number of tablets not taken during the previous month. Women were supplied with excess tablets, and the number of tablets returned served as a measure of compliance.

If anemia was detected in the routine 28-wk blood sample or if the woman's clinician considered her hemoglobin concentration to be too low, the woman was advised to purchase and take a high-dose iron supplement (containing \geq 80 mg/tablet) until the end of pregnancy. This was part of standard obstetric care provided by the woman's clinician independent of the trial. However, the women were encouraged to continue taking their assigned trial supplements. Thus, the women allocated to the iron-supplemented group received a total of 100 mg Fe/d if they were found to have anemia at 28 wk of gestation.

Assessments

Maternal hemoglobin concentrations at $<$ 20 and at 28 wk of gestation were obtained from hospital records. At delivery and at 6 mo postpartum, a 5-mL nonfasting blood sample was collected from the women to measure hemoglobin and serum ferritin as primary markers of iron status.

Hemoglobin concentrations were measured spectrophotometrically by using a Cell Dyn 4000 analyzer (Abbott Laboratories, Santa Clara, CA), and serum ferritin was determined by a microparticle enzyme immunoassay on an AxSYM Automated Analyzer (Abbott Laboratories, Abbott Park, IL). Analyses were completed within 3 h of collection by the Department of Hematology at Women's and Children's Hospital. The precision (CV) of the hemoglobin measurement was 0.9% and that of the serum ferritin measurement was 5.4%. Quality controls were used to check the accuracy of the analytic methods. Mean (\pm SD) quality-control values for hemoglobin (Cell Dyn 26 tri-level hematology control, lot CD091; Abbott Laboratories) and ferritin (Biorad Immuno Plus Control; Biorad Laboratories, Irvine, CA) were 135 ± 0.96 g/L and 53 ± 3.4 μ g/L, respectively, compared with the certified values of 137 ± 3.2 g/L and 57 ± 5.0 μ g/L, respectively. Definitions of iron status were based on the criteria determined by the Centers for Disease Control and Prevention, as summarized in **Table 1** (16). Maternal gastrointestinal side effects, such as nausea, heartburn, abdominal discomfort, constipation, and diarrhea, were assessed at 24 and 36 wk of gestation by use of a structured telephone questionnaire (7, 8).

Maternal serum zinc was assessed at delivery and at 6 mo postpartum. Blood was collected at the time of sampling by using trace-element-free evacuated containers (Becton Dickinson, Rutherford, NJ). Trace-element techniques were used during collection and analysis. After centrifugation ($500 \times g$, 20 min, 4 °C),



serum samples were stored at -20°C . Serum zinc was analyzed by flame atomic absorption spectrophotometry (model 800; Perkin-Elmer, Norwalk, CT) with use of a modification of the method of Smith et al (17). Serial replication of aliquots from a pooled serum sample and quality-control sera were used to check the precision and accuracy of the analytic method. The within-run CV for zinc in the pooled serum sample was 2% ($n = 67$ in each of the 7 runs). The mean (\pm SD) and CV for the quality control (bovine serum reference material no. 1598; National Institute of Standards and Technology, Gaithersburg, MD) were $13.8 \pm 0.2 \mu\text{mol/L}$ and 1.62% ($n = 37$), respectively, compared with the certified value of $13.6 \pm 0.1 \mu\text{mol/L}$.

Maternal indexes of well-being were assessed by use of a self-administered questionnaire, the SF-36, at 36 wk of gestation and at 6 wk and 6 mo postpartum (14, 18). Maternal dietary iron intake was assessed by use of an iron-specific validated food-frequency questionnaire at 20 and 36 wk of gestation (19).

Pregnancy outcomes were obtained from each woman's medical records. These included type of birth, blood loss at delivery, gestational age, birth weight, birth length, birth head circumference, placental weight, Apgar scores, and level of nursery care.

Sample size

From a systematic review of previous trials that treated women with high doses of iron (4) and local pregnancy surveillance data (3), we estimated that the rate of IDA in our population of pregnant women would be $\approx 11.5\%$. We hypothesized that 20 mg Fe/d (aimed at meeting the RDI) would reduce the rate of IDA from 11.5% to 3%, requiring 166 women per dietary group with 85% power, $\alpha = 0.05$. Similarly, treatment with high-dose iron is reported to decrease the proportion of women with ID from 73% to 22% at the end of pregnancy (4). We conservatively estimated that we could detect a reduction in the rate of ID from 30% to 15% with 138 women per group with 85% power, $\alpha = 0.05$. Gastrointestinal symptoms are reported to occur in 25–40% of persons treated with high-dose iron supplements compared with 10% of persons treated with placebo (7, 8). With 199 women per group, we could detect a minimum increase in gastrointestinal side effects from 10% to 20%, with 80% power and $\alpha = 0.05$. We thus planned to recruit 215 women per group to allow for withdrawals.

Statistical methods

The effect of iron supplementation on maternal iron status, SF-36 indexes of well-being, and maternal zinc status was assessed by *t* test. Ferritin data were log transformed for analysis. Chi-square tests were used to compare the proportions of IDA, ID, and gastrointestinal side effects between women allocated to iron treatment and those allocated to placebo. Hemoglobin data at each of the 3 postbaseline assessment times were analyzed by analysis of covariance with a Bonferroni adjustment to the significance. All available data were used for intention-to-treat analyses. All analyses were conducted by using SPSS for WINDOWS, version 10.0 (SPSS Inc, Chicago).

RESULTS

Participant flow and data for intention-to-treat analysis

A total of 498 eligible women were approached to enter the trial between December 1997 and April 1999. As shown in **Figure 1**, 68 (14%) women declined to participate; 430 (86%)

women were randomly allocated to either iron ($n = 216$) or placebo ($n = 214$) tablets. During the supplementation phase of the trial, 14 (6%) women from the iron-supplemented group and 18 (8%) women from the placebo group withdrew their consent for blood sampling and completing the questionnaires and stopped taking their allocated supplements. Two (1%) women from the iron-supplemented group and 3 (1%) from the placebo group gave birth before 35 wk of gestation, which left 200/216 (93%) women from the iron-supplemented group and 193/214 (90%) women from the placebo group to complete the 36-wk assessment for gastrointestinal side effects.

At the time of delivery, 200/216 (94%) and 193/214 (90%) maternal hemoglobin samples were available from the iron-supplemented and placebo groups, respectively, and 186/216 (86%) and 176/214 (82%) ferritin samples were available from the iron-supplemented and placebo groups, respectively. Pregnancy outcome data were available for all women and all infants ($n = 220$ in the iron-supplemented group and $n = 215$ in the placebo group). At the 6-mo postpartum follow-up, 189/216 (88%) maternal hemoglobin samples and 190/216 (88%) maternal ferritin samples were available for analysis from the iron-supplemented group and 177/214 (83%) maternal hemoglobin and ferritin samples were analyzed from the placebo group.

Baseline characteristics, dietary iron intake, and compliance

The sociodemographic characteristics of the women in the 2 groups were not significantly different (**Table 2**). Most women were white and were, on average, 28 y of age at study entry. About one-half of the women and their partners had completed secondary education and about one-fifth of the women were smokers. The body mass index of the women at the time they first attended the antenatal clinic was not significantly different between the groups. Iron intake from food at 20 and 36 wk of gestation also did not differ significantly between the groups [$13.0 \pm 5.4 \text{ mg/d}$ in the iron-treated group ($n = 198$) compared with $13.6 \pm 5.4 \text{ mg/d}$ in the placebo group ($n = 192$) at 20 wk, and $14.6 \pm 6.5 \text{ mg/d}$ in the iron-treated group ($n = 189$) compared with $14.3 \pm 6.4 \text{ mg/d}$ in the placebo group ($n = 184$) at 36 wk]. There were no significant differences in social or demographic characteristics between the women who successfully completed the trial and those with missing data for primary outcome measures.

The back-count of tablets collected from 174 women in the iron-supplemented group and 164 women in the placebo group showed that 86% of women in the iron-supplemented group and 85% of women in the placebo group took their allocated supplement daily. There was a strong correlation between the noncompliance data based on the tablet back-count and that based on the number of tablets the women reported not taking during the monthly telephone calls ($r = 0.86$, $P < 0.001$, $n = 338$).

At 6 wk postpartum, 374 women responded to our question regarding the success of blinding. A total of 91 of 191 (48%) women correctly identified that they had received iron, and 94 of 183 (51%) identified that they were in the placebo group.

Primary efficacy outcomes: maternal iron deficiency and iron deficiency anemia

At the end of pregnancy, fewer women in the iron-supplemented group than in the placebo group had IDA (3% compared with 11%; $P < 0.005$; **Table 3**). Similarly, the rate of ID was lower in the iron-supplemented group than in the placebo group (35% compared with 58%; $P < 0.001$). Interestingly, the differences in iron status occurred even though fewer women in the iron-supplemented

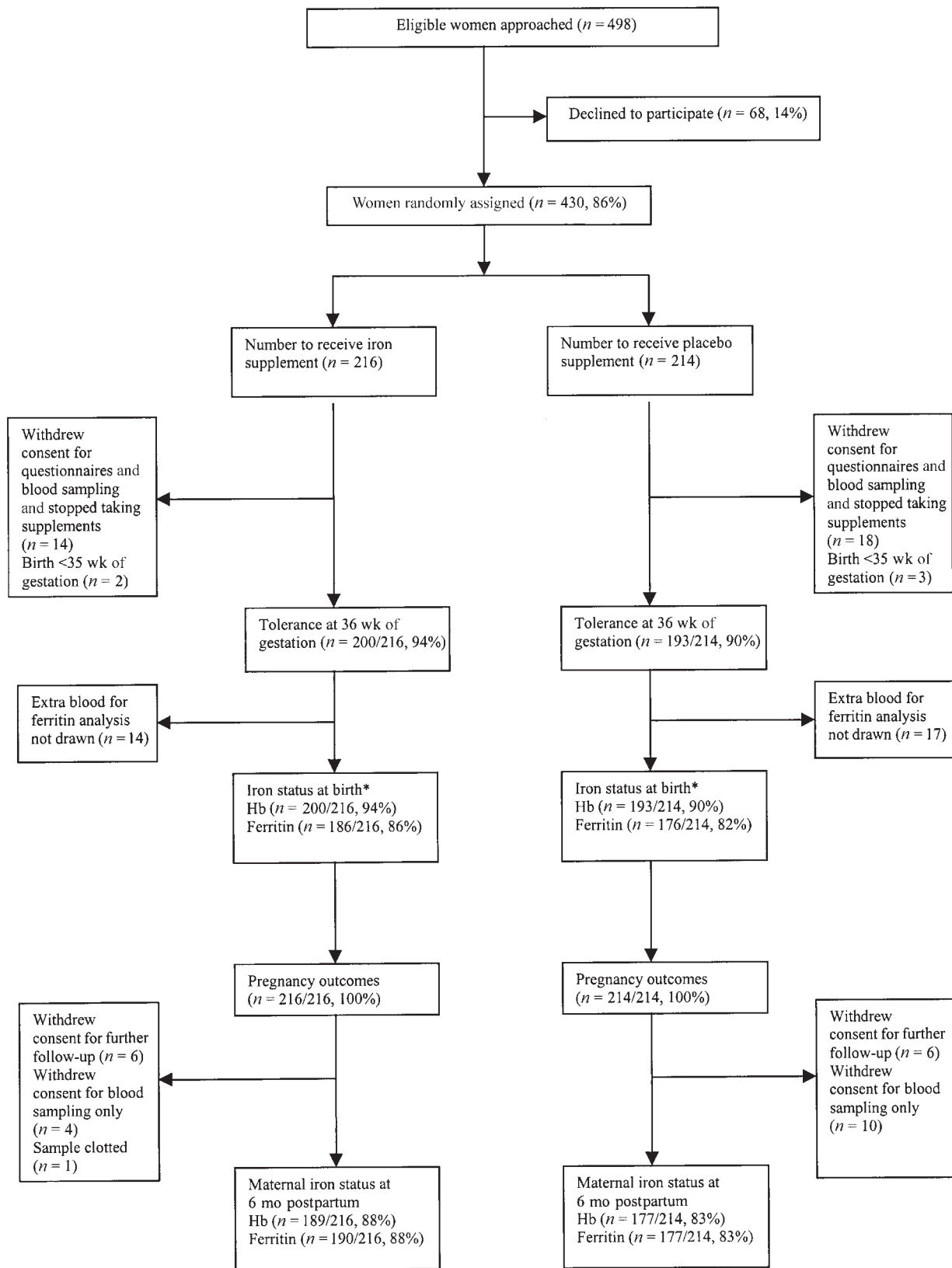


FIGURE 1. Trial profile. Hb, hemoglobin. *The 200 women from the iron-supplemented group and the 193 women from the placebo group with hemoglobin measurements at the time of delivery are not the same women who responded to the tolerance questions at 36 wk of gestation. Two women from the iron-supplemented group and 3 women from the placebo group were different at 36 wk of gestation and at the time of delivery.

TABLE 2Characteristics of the women participating in the trial at entry¹

| Variable | Iron-supplemented group (n = 216) | Placebo group (n = 214) |
|--|--------------------------------------|----------------------------|
| Maternal age (y) | 28.5 ± 5 ² | 28.0 ± 5 |
| <20 y [n (%)] | 6 (2.8) | 6 (2.8) |
| 20–29 y [n (%)] | 128 (59.3) | 132 (61.7) |
| 30–39 y [n (%)] | 77 (35.6) | 72 (33.6) |
| ≥40 y [n (%)] | 5 (2.3) | 4 (1.9) |
| Race of mother [n (%)] | | |
| White | 206 (95.4) | 204 (95.3) |
| Aboriginal | 2 (0.9) | 7 (3.3) |
| Asian | 5 (2.3) | 3 (1.4) |
| Other or unknown | 3 (1.4) | 0 (0.0) |
| Nulliparous [n (%)] | 103 (47.7) | 100 (46.7) |
| Multiparous [n (%)] | 113 (52.3) | 114 (53.3) |
| Maternal BMI (kg/m ²) | 26.0 ± 5.7 | 25.5 ± 5.2 |
| Maternal smoking [n (%)] | 41 (19.0) | 43 (20.1) |
| Occupational score of mother ³ | 5.3 ± 0.8 | 5.3 ± 0.9 |
| Occupational score of partner ³ | 4.8 ± 1.1 [208] ⁴ | 4.9 ± 1.2 [204] |
| Highest education level of mother [n (%)] | | |
| Year 10 or less | 26 (12.0) | 33 (15.4) |
| Year 11 | 58 (26.9) | 59 (27.6) |
| Year 12 | 71 (32.9) | 60 (28.0) |
| Trade certificate or diploma | 11 (5.1) | 16 (7.5) |
| Tertiary degree | 45 (20.9) | 44 (20.6) |
| Unknown | 5 (2.3) | 2 (0.9) |
| Highest education level of partner [n (%)] | | |
| Year 10 or less | 28 (13.0) | 36 (16.8) |
| Year 11 | 38 (17.6) | 44 (20.6) |
| Year 12 | 61 (28.2) | 47 (22.0) |
| Trade certificate or diploma | 39 (18.1) | 25 (11.7) |
| Tertiary degree | 37 (17.1) | 53 (24.8) |
| Unknown | 13 (6.0) | 9 (4.2) |

¹There were no significant differences between the groups.² $\bar{x} \pm$ SD.³Ranked according to the scale published by Daniel (15).⁴n in brackets.

group than in the placebo group were prescribed and treated with high-dose iron tablets containing 80–105 mg elemental iron (relative risk: 0.59; 95% CI: 0.41, 0.84; $P < 0.001$; Table 3). The effectiveness of low-dose iron supplementation was highlighted by the change in hemoglobin concentrations during the latter half of pregnancy. At both 28 wk of gestation and at delivery, hemoglobin concentrations were higher in the iron-supplemented group than in the placebo group, even after adjustment for the baseline (20 wk of gestation) hemoglobin value.

At 6 mo postpartum (ie, 6 mo after the end of supplementation), fewer women in the iron-supplemented group than in the placebo group had ID (16% compared with 29%; $P < 0.005$; Table 3). The rates of anemia and of IDA did not differ significantly between groups at 6 mo postpartum.

Primary tolerance outcomes

The prevalence of nausea, stomach pain, heartburn, vomiting, rash, and hard stools and the frequency of bowel actions was not significantly different between women in the iron-supplemented group and those in the placebo group at both 24 and 36 wk of gestation (Table 4).

Because there were no significant differences in any side effects between the iron-supplemented and the placebo groups, we conducted a secondary exploratory analysis to assess the effect of high-dose iron supplements on tolerance outcomes at 36 wk of gestation. Women who took high-dose iron supplements reported a higher prevalence of black stools (10/93, or 10.8%, compared with 1/298, or 0.3%; $P < 0.001$) and hard stools (21/93, or 22.6%, compared with 38/298, or 12.7%; $P < 0.05$) than did the women who received only low-dose iron or placebo treatment.

Secondary outcomes

SF-36 health concepts

There were no significant differences in any of the 8 health concepts measured by the SF-36 between the women in the iron-supplemented group and those in the placebo group at 36 wk of gestation, 6 wk postpartum, or 6 mo postpartum (Figure 2). Women in week 36 of gestation had lower (worse) scores overall for health concepts related to physical functioning and role, bodily pain, vitality, and social functioning than the age-standardized population norms for women (20). By 6 mo postpartum, the women in the trial reported better scores than the population norms for physical functioning and role, bodily pain, and general health.

Maternal serum zinc status

There were no significant differences in serum zinc concentrations between the women in the iron-supplemented group and those in the placebo group at delivery or at 6 mo postpartum (Table 4). At the end of pregnancy, 40/79 (51%) women in the iron-supplemented group and 46/78 (59%) women in the placebo group had a serum zinc concentration $< 9.18 \mu\text{mol/L}$, which is indicative of suboptimal status (21). At 6 mo postpartum, 11/160 (7%) and 15/146 (10%) women in the iron-supplemented and placebo groups, respectively, had low serum zinc status on the basis of a cutoff for nonfasting blood samples from nonpregnant women of $9.95 \mu\text{mol/L}$ (22).

Pregnancy outcomes

Most women had a normal vaginal birth. Mode of delivery or the amount of blood loss at delivery did not differ significantly between the groups (Table 5). There were 2 stillbirths caused by an abortion with a severe antepartum hemorrhage (iron-supplemented group) and a termination for trisomy 21 (placebo group). The single neonatal death (infant born at 22 wk with bilateral intrauterine pneumonia) occurred in the iron-supplemented group. Most infants were born at term with birth weights > 2500 g. There were no significant differences in gestational age at birth, birth weight, birth length, birth head circumference, Apgar scores, or the level of neonatal care required between the iron-supplemented and placebo groups (Table 5). The pregnancy outcome data for women participating in our trial were not dissimilar to outcome data of all births reported in South Australia over the period of the trial (23).

DISCUSSION

Our trial showed that routine supplementation of well-nourished pregnant women with only 20 mg Fe/d is highly effective at preventing ID and IDA. In fact, the prevalence of IDA at the end of pregnancy was reduced from 10.8% to 3%. This result occurred against a background of all women being screened for anemia at 28 wk of gestation and being treated with high-dose iron if the

TABLE 3
Iron status of women¹

| Variable | Iron-supplemented group | Placebo group | RR or MD (95% CI) ² |
|--|----------------------------|----------------|--------------------------------|
| Maternal status at baseline | | | |
| Hb at < 20 wk of gestation (g/L) | 131 ± 8 [215] ³ | 130 ± 8 [213] | 1.0 (−0.6, 2.6) |
| Maternal status at 28 wk of gestation | | | |
| Hb (g/L) | 120 ± 8 [206] | 116 ± 9 [205] | 3.4 (1.7, 5.3) ⁴ |
| No. with anemia | 20/206 | 51/205 | 0.39 (0.24, 0.63) ⁴ |
| No. treated with high-dose iron because of low Hb at 28 wk | 38/216 | 64/214 | 0.59 (0.41, 0.84) ⁴ |
| Maternal status at delivery | | | |
| Hb (g/L) | 127 ± 13 [200] | 120 ± 12 [193] | 6.9 (4.4, 9.3) ⁴ |
| Serum ferritin (μg/L) | 21 ± 18 [186] | 14 ± 10 [176] | 7.1 (4.0, 10.2) ⁴ |
| No. with ID | 65/186 | 102/176 | 0.60 (0.48, 0.76) ⁴ |
| No. with anemia | 14/200 | 30/193 | 0.45 (0.25, 0.82) ⁵ |
| No. with IDA | 6/198 | 20/185 | 0.28 (0.12, 0.68) ⁶ |
| Maternal status at 6 mo postpartum | | | |
| Hb (g/L) | 135 ± 9 [189] | 134 ± 8 [177] | 1.6 (−0.1, 3.3) |
| Serum ferritin (μg/L) | 34 ± 24 [190] | 26 ± 19 [177] | 7.9 (3.5, 12.3) ⁴ |
| No. with ID | 31/190 | 51/177 | 0.57 (0.38, 0.84) ⁶ |
| No. with anemia | 7/189 | 8/177 | 0.82 (0.30, 2.21) |
| No. with IDA | 5/190 | 3/177 | 1.55 (0.38, 6.40) |

¹RR, relative risk; MD, mean difference; Hb, hemoglobin; ID, iron deficiency; IDA, iron deficiency anemia.²Statistical analyses represent comparison between groups at the specific assessment time periods with Bonferroni adjustments to the significance.³ $\bar{x} \pm SD$; *n* in brackets.⁴*P* < 0.001.⁵*P* < 0.01.⁶*P* < 0.005.**TABLE 4**
Potential adverse effects of iron supplementation¹

| Variable | Iron-supplemented group | Placebo group | RR or MD (95% CI) |
|--|-------------------------------|--------------------|--------------------|
| Tolerance at 24 wk of gestation (<i>n</i> /total <i>n</i>) | | | |
| Nausea | 51/204 | 45/204 | 1.13 (0.80, 1.61) |
| Stomach pain | 47/204 | 39/204 | 1.21 (0.83, 1.76) |
| Heartburn | 100/204 | 100/204 | 1.00 (0.82, 1.22) |
| Vomiting | 21/204 | 27/204 | 0.78 (0.45, 1.33) |
| Rash | 14/204 | 14/204 | 1.00 (0.49, 2.04) |
| Black stool | 0/204 | 0/204 | — |
| Hard stool | 36/204 | 32/204 | 1.12 (0.73, 1.74) |
| Bowel actions | | | |
| Daily | 146/204 | 148/203 | 0.98 (0.87, 1.11) |
| Every other day | 40/204 | 43/203 | 0.93 (0.63, 1.36) |
| ≤ 3 times/wk | 18/204 | 12/203 | 1.49 (0.74, 3.02) |
| Tolerance at 36 wk of gestation (<i>n</i> /total <i>n</i>) | | | |
| Nausea | 58/200 | 54/193 | 1.04 (0.76, 1.42) |
| Stomach pain | 70/200 | 57/193 | 1.19 (0.89, 1.58) |
| Heartburn | 136/200 | 133/193 | 0.99 (0.86, 1.13) |
| Vomiting | 24/200 | 26/193 | 0.89 (0.53, 1.50) |
| Rash | 15/200 | 12/193 | 1.21 (0.58, 2.51) |
| Black stool | 3/200 | 8/191 | 0.36 (0.10, 1.33) |
| Hard stool | 25/200 | 34/191 | 0.70 (0.44, 1.13) |
| Bowel actions | | | |
| Daily | 139/200 | 149/192 | 0.90 (0.79, 1.01) |
| Every other day | 53/200 | 40/192 | 1.27 (0.89, 1.82) |
| ≤ 3 times/wk | 8/200 | 3/192 | 2.56 (0.69, 9.51) |
| Serum zinc (μmol/L) | | | |
| At delivery | 9.58 ± 2.48 [79] ² | 9.06 ± 2.13 [78] | 0.52 (−0.21, 1.4) |
| At 6 mo postpartum | 12.43 ± 2.32 [160] | 12.06 ± 2.17 [146] | 0.37 (−0.13, 0.88) |

¹RR, relative risk; MD, mean difference. There were no significant differences between the groups.² $\bar{x} \pm SD$; *n* in brackets.

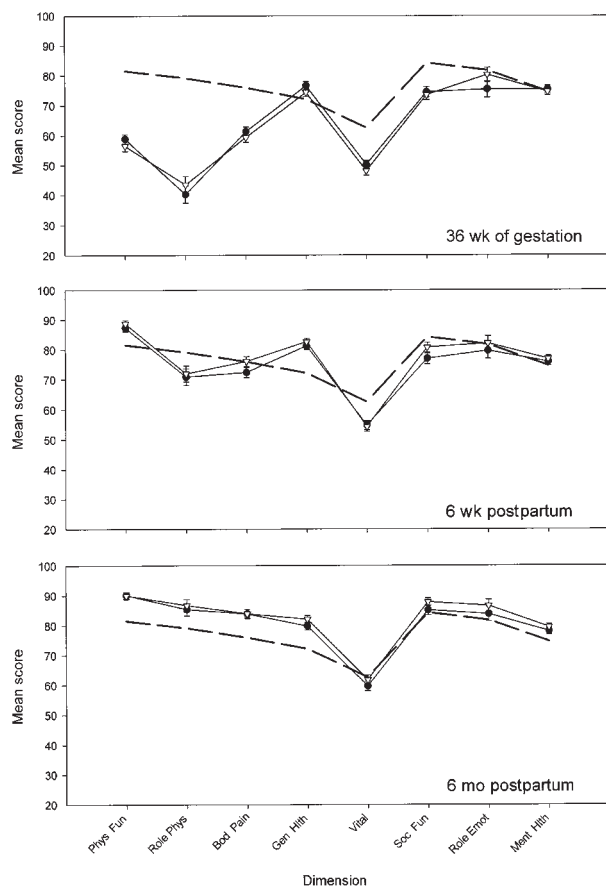


FIGURE 2. Mean (± 1 SEM) scores on the 8 health concepts of the SF-36 questionnaire (14) for women in the iron-supplemented (\bullet) and placebo (∇) groups. Phys Fun, physical functioning, which measures limitations in physical activities because of health problems; Role Phys, role-physical, which measures limitations in usual role activities because of physical health problems; Bod Pain, bodily pain; Gen Hlth, general health; Vital, vitality, which measures energy and fatigue; Soc Fun, social functioning, which measures limitations in social activities because of physical or emotional problems; Role Emot, role-emotional, which measures limitations in usual role activities because of emotional problems; Ment Hlth, general mental health, which measures psychological distress and well-being. Higher scores indicate better well-being on each health concept. The dashed line represents the mean age-standardized values for Australian women determined from the National Health Survey, which included responses on the SF-36 from 9612 women (20).

screening result was positive. This indicates that the practice of screening and treating is inadequate for maintaining good iron nutrition during pregnancy because an intervention applied against this background was clearly effective at improving iron status and preventing deficiency. Our trial also showed that routine low-dose supplementation is well tolerated and is not associated with side effects. Collectively, these data provide some of the first high-quality evidence required to support the safety and efficacy of low-dose iron supplementation during pregnancy.

Few investigations of the effects of low-dose iron supplementation during pregnancy have been carried out (24–26). Eskeland et al (24) reported that women randomly allocated to supplements

containing 27 mg elemental iron had better iron status throughout pregnancy than did women in the placebo group. However, studies that compared low-dose with high-dose supplementation have reported contrasting results. Thomsen et al (26) suggested that supplementation with 18 mg Fe/d was less effective than 100 mg Fe/d at maintaining serum ferritin and hemoglobin, whereas Chanarin and Rothman (25) reported that pregnant women given 30 mg Fe/d maintained their hemoglobin concentrations as effectively as did women supplemented with 60 or 120 mg Fe/d. Although these intervention studies were small (24–26) and not always randomized (25), they provide some clues that routine, low-dose supplementation may be efficient and effective at ensuring optimal iron nutrition during pregnancy. In our trial, the mean differences in hemoglobin and serum ferritin between the iron-supplemented and placebo groups at the end of pregnancy [hemoglobin: 7 g/L (95% CI: 5, 9 g/L); ferritin: 7 μ g/L (95% CI: 4, 10 μ g/L)] were remarkably similar to the weighted mean differences reported in a systematic review of randomized trials, most of which provided 100 mg elemental iron/d [hemoglobin: 8 g/L (95% CI: 7, 10 g/L); ferritin: 11 μ g/L (95% CI: 10, 12 μ g/L)] (4). Collectively, these data indicate that routine supplementation with as little as 20 mg Fe/d offers a viable public health strategy for preventing IDA during pregnancy in industrialized countries.

Six months after the end of supplementation, women in the present study who had been treated with iron during pregnancy had higher serum ferritin concentrations and a lower rate of ID than did placebo-treated women. These findings agree with those of other randomized trials of iron supplementation during pregnancy that assessed maternal iron status in the postpartum period (24, 27–30). Thus, maintaining good iron nutrition during pregnancy may be an important mechanism for achieving restoration of maternal iron stores.

The commonly cited risks of iron supplementation include gastrointestinal symptoms and interference with the absorption of other trace minerals, notably zinc. Our data indicated that taking iron at a dosage of 20 mg/d does not induce gastrointestinal side effects. In fact, only the women prescribed a high dosage of iron (≥ 80 mg/d) as part of the obstetric care offered by their clinicians reported an increased prevalence of black stool and hard stool. These findings are consistent with studies of male blood donors that suggested that side effects are dose related and usually occur at higher doses (7, 8). Similarly, supplementing with < 30 mg Fe/d is thought to not affect serum zinc concentrations (2, 9, 31). Ours is the first randomized trial in an industrialized country to show that low-dose iron supplementation has no adverse effect on the serum zinc concentrations of pregnant women. In summary, there were few side effects of low-dose iron supplementation during pregnancy, which may facilitate compliance. It is also timely to reassess the safety of routine iron supplementation with the higher doses that may be received through standard clinical practice.

The general health effects of iron deficiency in pregnant women have been identified as an area of research priority (32). We found no significant differences in the 8 health concepts of the SF-36 between iron-treated and untreated women. Hemminki and Rimpela (33), who compared routine and selective iron supplementation (100 mg/d) in a large randomized trial in Finland, also reported no differences in self estimates of well-being and fatigue and in the number of sick days between groups. It may be that the effects of iron deficiency on general health and well-being are subtle and are not apparent until more severe anemia is present or that standardized quality-of-life questionnaires such as the SF-36 are not sensitive enough to measure the effects of iron deficiency (20).



TABLE 5
Pregnancy outcomes of the trial participants¹

| Variable | Iron-supplemented group (n = 216) | Placebo group (n = 214) | All births in SA for 1999 ² |
|---|--------------------------------------|----------------------------|---|
| Mode of birth [n (%)] | | | |
| Normal vaginal | 131 (60.6) | 144 (67.3) | 11 353 (62.3) |
| Instrumental vaginal | 34 (15.7) | 23 (10.7) | 2336 (12.6) |
| Caesarean delivery | 51 (23.6) | 47 (22.0) | 4544 (24.5) |
| Blood loss at delivery (mL) | 366 ± 272 [204] ³ | 324 ± 233 [201] | — |
| Plurality [n (%)] | | | |
| Singleton | 212 (96.4) | 213 (99.1) | 17 949 (96.9) |
| Multiple | 8 (3.6) | 2 (0.9) | 570 (3.1) |
| Condition at birth [n (%)] | | | |
| Live birth | 219 (99.5) | 214 (99.5) | 18 404 (99.4) |
| Stillbirth | 1 (0.5) | 1 (0.5) | 115 (0.6) |
| Neonatal death [n (%)] | 1 (0.5) | 0 (0) | 88 (0.5) |
| Sex [n (%)] | | | |
| Male | 113 (51.4) | 105 (48.8) | 9472 (51.1) |
| Female | 107 (48.6) | 110 (51.2) | 9047 (48.9) |
| Gestational age at birth (wk) | 39.4 ± 2.2 | 39.2 ± 2.3 | — |
| Birth weight [n (%)] | | | |
| <2500 g | 12 (5.4) | 9 (4.2) | 1218 (6.6) |
| 2500–3499 g | 105 (47.7) | 106 (49.3) | 9435 (50.9) |
| 3500–4499 g | 101 (45.9) | 96 (44.7) | 7518 (40.6) |
| ≥ 4500 g | 2 (0.9) | 4 (1.9) | 348 (1.9) |
| Birth weight (g) | 3406 ± 597 | 3449 ± 580 | — |
| Birth length (cm) | 49.9 ± 3.2 | 50.0 ± 2.8 | — |
| Birth head circumference (cm) | 34.4 ± 2.2 | 34.7 ± 2.1 | — |
| Apgar score < 7 at 5 min [n (%)] | 3 (1.4) | 4 (1.9) | — |
| Level of nursery care (used by all live births) [n (%)] | | | |
| Level I only | 185 (84.5) | 176 (82.2) | 15 312 (83.2) |
| Level II | 39 (17.8) | 43 (20.1) | 3055 (16.6) |
| Level III | 6 (2.7) | 7 (3.3) | 481 (2.6) |

¹There were no significant differences between the groups.


²Pregnancy outcomes in South Australia (SA) in 1999 (23).

³ \bar{x} ± SD; n in brackets.

We also found no significant differences in pregnancy outcomes between the iron-supplemented and placebo groups. Although this is not surprising given the low prevalence of infants born with a low birth weight (<2500 g), it does raise the question of whether the cutoffs used for iron deficiency reflect a true deficiency that is associated with functional changes in health outcomes. It may be that we need to reevaluate the definitions of iron deficiency during pregnancy or that changes in health outcomes associated with iron deficiency are more obvious in population groups with less healthy pregnancies and poorer pregnancy outcomes.

The women included in this trial were typical of Australian pregnant women. Their demographic characteristics and pregnancy outcomes were not significantly different from women in South Australia who gave birth during the course of the trial (Table 5). Furthermore, the iron intakes from food during weeks 20 and 36 of gestation were remarkably similar to those reported by pregnant women as part of the 1995 National Nutrition Survey (13) as well as in other dietary surveys of women in industrialized countries (34). It is therefore likely that the results observed in this trial are applicable to broader populations of women in industrialized countries.

The Australian RDI for iron during pregnancy (22–36 mg/d) has been estimated as the range of iron intake needed to achieve iron balance and prevent 97% of healthy, well-nourished women

from developing IDA (12). Our trial showed that low-dose supplements aimed at “topping-up” intake from food to the RDI resulted in 3% of women with IDA (low ferritin and low hemoglobin) at the end of pregnancy. This finding validates the RDI for iron during pregnancy, which to our knowledge has not been previously tested in a randomized controlled trial. Although we do not yet fully understand the clinical consequences of preventing IDA for pregnancy outcomes and the long-term health of mothers and children, the importance of our findings are underscored by the fact that the supplement intervention resulted in both short- and long-term changes in iron status. It therefore seems prudent to implement public health strategies aimed at preventing the most common micronutrient deficiency worldwide, while further investigations aim at quantifying the clinical effects on mothers and children. 

We thank Mandy O’Grady, Jo Collins, Heather Garreffa, Sarah Russell, Lyn Pullen, Helen Blake, Glenda Dandy, Bronwen Paine, David Ellis, Steve Tiszavari, the staff of the delivery suite, and the staff of the core laboratory at the Women’s & Children’s Hospital for their administrative, clinical, and technical support.

MM designed the study and wrote the report with contributions from all coauthors. MM (chair), CAC, and RAG were the committee who monitored and managed the trial. RSG and CMS were responsible for the serum zinc analyses. The authors had no known conflicts of interest.

REFERENCES

1. Aggett P. Iron and women in the reproductive years. In: *The British Nutrition Foundation's Task Force, ed. Iron: nutritional and physiological significance*. 1st ed. London: Chapman and Hall, 1995: 110-8.
2. Subcommittee on Nutritional Status and Weight Gain During Pregnancy, Subcommittee on Dietary Intake and Nutrient Supplements During Pregnancy, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Iron nutrition during pregnancy*. In: *Nutrition and Pregnancy: part I, weight gain, and part II, nutrient supplements*. 1st ed. Washington, DC: National Academy Press, 1990:272-98.
3. Chan A, Scott J, McCaul K, Keane R. *Pregnancy outcome in South Australia 1997*. Adelaide, Australia: South Australian Health Commission, 1998.
4. Mahomed K. *Iron supplementation in pregnancy (Cochrane Review)*. In: *The Cochrane Library*. Issue 4. Oxford, United Kingdom: Update Software, 2001.
5. Yip R, Dallman PR. Iron. In: Ziegler EE, ed. *Present knowledge in nutrition*. 7th ed. Washington, DC: ILSI Press, 1996:277-92.
6. US Preventive Services Task Force. Routine iron supplementation during pregnancy. *JAMA* 1993;270:2848-54.
7. Hallberg L, Ryttinger L, Solvell L. Side-effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. *Acta Med Scand Suppl* 1966;459:3-10.
8. Solvell L. Oral iron therapy-side effects. In: Hallberg L, Harwerth HG, Vannotti A, eds. *Iron deficiency: pathogenesis, clinical aspects, therapy*. 1st ed. London: Academic Press, 1970:573-83.
9. Solomons NW. Competitive interaction of iron and zinc in the diet: consequences for human nutrition. *J Nutr* 1986;116:927-35.
10. Litovitz TL, Holm KC, Clancy C, Schmitz BF, Clark LR, Oderda GM. 1992 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1993; 11:494-555.
11. Enkin M, Keirse MJNC, Renfrew M, Neilson J. Dietary modification in pregnancy. In: Enkin E, ed. *A guide to effective care in pregnancy and childbirth*. 2nd ed. Oxford, United Kingdom: Oxford University Press, 1995:28-33.
12. National Health & Medical Research Council. *Recommended dietary intakes for use in Australia, 1991*. Canberra, Australia: Australian Government Publishing Service, 1991.
13. McLennan W, Podger A. *National Nutrition Survey: nutrient intakes and physical measurements Australia 1995*. Canberra, Australia: Australian Bureau of Statistics, 1998.
14. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
15. Daniel A. *Power, privilege and prestige: occupations in Australia*. 1st ed. Melbourne: Longman-Cheshire, 1983.
16. Centers for Disease Control. CDC criteria for anemia in children and childbearing-aged women. *MMWR Morbid Mortal Weekly Rep* 1989;38:400-4.
17. Smith JC Jr, Butrimovitz GP, Purdy WC. Direct measurement of zinc in plasma by atomic absorption spectroscopy. *Clin Chem* 1979;25: 1487-91.
18. McHorney CA, Ware JE Jr, Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. *Med Care* 1992;30:MS253-65.
19. Schilling MJ, Makrides M. Validation of a checklist to assess iron intake of pregnant women. *Proceedings of the 3rd Annual Congress of the Perinatal Society of Australia and New Zealand*. Parramatta, Australia: Perinatal Society of Australia and New Zealand, 1999:251.
20. Australian Bureau of Statistics. *1995 National Health Survey: SF-36 population norms Australia*. Canberra, Australia: Australian Bureau of Statistics, 1997. (ABS catalogue no. 4399.0.)
21. Jameson S. Zinc status in pregnancy: the effect of zinc therapy on perinatal mortality, prematurity, and placental ablation. *Ann NY Acad Sci* 1993;678:178-92.
22. Pilch SM, Senti FR. Analysis of zinc data from the second National Health and Nutrition Examination Survey (NHANES II). *J Nutr* 1985; 115:1393-7.
23. Chan A, Scott J, Nguyen AM, Keane R. *Pregnancy outcome in South Australia 1999*. Adelaide, Australia: Department of Human Services, 1999.
24. Eskeland B, Malterud KE, Ulvik RJ, Hunskaar S. Iron supplementation in pregnancy: is less enough? A randomized, placebo controlled trial of low dose iron supplementation with and without heme iron. *Acta Obstet Gynecol Scand* 1997;76:822-8.
25. Chanarin I, Rothman D. Further observations on the relation between iron and folate status in pregnancy. *Br Med J* 1971;2:81-4.
26. Thomsen JK, Prien-Larsen JC, Devantier A, Fogh-Andersen N. Low dose iron supplementation does not cover the need for iron during pregnancy. *Acta Obstet Gynecol Scand* 1993;72:93-8.
27. Taylor DJ, Mallen C, McDougall N, Lind T. Effect of iron supplementation on serum ferritin levels during and after pregnancy. *Br J Obstet Gynaecol* 1982;89:1011-7.
28. Milman N, Agger AO, Nielsen OJ. Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women. *Dan Med Bull* 1991;38:471-6.
29. Puolakka J, Janne O, Pakarinen A, Jarvinen PA, Vihko R. Serum ferritin as a measure of iron stores during and after normal pregnancy with and without iron supplements. *Acta Obstet Gynecol Scand Suppl* 1980;95:43-51.
30. Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Hercberg S. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. *Am J Clin Nutr* 1997;66: 1178-82.
31. Hambidge KM, Krebs NF, Sibley L, English J. Acute effects of iron therapy on zinc status during pregnancy. *Obstet Gynecol* 1987; 70:593-6.
32. Stoltzfus RJ. Iron-deficiency anemia: reexamining the nature and magnitude of the public health problem. Summary: implications for research and programs. *J Nutr* 2001;131:697S-700S.
33. Hemminki E, Rimpela U. A randomized comparison of routine versus selective iron supplementation during pregnancy. *J Am Coll Nutr* 1991;10:3-10.
34. Schofield C, Stewart J, Wheeler E. The diets of pregnant and post-pregnant women in different social groups in London and Edinburgh: calcium, iron, retinol, ascorbic acid and folic acid. *Br J Nutr* 1989; 62:363-77.