Symposium: Improving Adolescent Iron Status before Childbearing

Anemia, Iron and Pregnancy Outcome[1,2]

Theresa O. Scholl[3] and Thomas Reilly*

*Department of Obstetrics and Gynecology, University of Medicine and Dentistry of New Jersey-SOM and *Department of Primary Care, University of Medicine and Dentistry of New Jersey-SHRP, Stratford, NJ 08084*

ABSTRACT When maternal anemia is diagnosed before midpregnancy, it has been associated with an increased risk of preterm delivery. Maternal anemia detected during the later stages of pregnancy, especially the third trimester, often reflects the expected (and necessary) expansion of maternal plasma volume. Third-trimester anemia usually is not associated with increased risk of preterm delivery. High hemoglobin concentration, elevated hematocrit and increased levels of serum ferritin late in pregnancy, however, all have been associated with increased preterm delivery. This increased risk may reflect in part the failure to expand maternal plasma volume adequately, thus diminishing appropriate placental perfusion. Although controlled trials of iron supplementation during pregnancy have consistently demonstrated positive effects on maternal iron status at delivery, they have not demonstrated reductions in factors that are associated with maternal anemia, i.e., increased risk of preterm delivery and infant low birth weight. One reason for discordant findings may be the exclusion of many gravidas with iron deficiency from these trials or the data concerning gravidas with pregnancy outcomes such as preterm delivery from the analysis. Finally, recent concerns have been voiced about harmful effects of iron supplementation during pregnancy. No adverse effects of iron supplementation on pregnancy outcome have been demonstrated to date. Questions about the efficacy of iron supplementation during pregnancy for reducing adverse outcomes such as preterm delivery and side effects from iron supplementation, including the potential for oxidation of lipids and DNA, require further research in iron-deficient women. J. Nutr. 130: 443S–447S, 2000.

KEY WORDS: • *iron* • *anemia* • *hemoglobin* • *ferritin* • *pregnancy outcome*

Maternal anemia during early gestation and poor pregnancy outcome

The relationship between anemia or iron deficiency anemia and increased risk of preterm delivery (<37 wk gestation) has been supported by several studies (Klebanoff et al. 1991; Lu et al. 1991, Murphy et al. 1986, Scholl et al. 1992, Scholl and Hediger 1994, Zhou et al. 1998). Studies have attempted to distinguish actual iron deficiency anemia from the normal influences of pregnancy-associated hemodilution as gestation proceeds by studying pregnant women early in gestation.

In a study of 44,000 pregnancies from Cardiff, Wales, Murphy et al. (1986) examined the prevalence of anemia in women who sought antenatal care by 24 wk gestation. Increased risk of preterm delivery was associated with low hemoglobin when women received antenatal care during the first trimester or after midpregnancy (wk 20). For women beginning antenatal care during the first trimester and between 20 and 24 wk gestation, an increased risk for preterm delivery was also associated with high hemoglobin concentrations (>145 g/L). Thus a U-shaped distribution existed for this cohort, with higher rates of preterm delivery at both ends of the hemoglobin range, irrespective of the gestation at booking. Although the study population had similar smoking rates, this factor and others that influence risk for preterm birth were uncontrolled.

Klebanoff et al. (1991) used a case-control design to examine the relationship between second and third trimester hematocrit and risk of preterm birth in >1700 gravidas from the Kaiser Permanente Birth Defects Study. For biweekly intervals between 13 and 26 wk gestation, odds for preterm delivery with anemia were almost doubled (adjusted odds ratio = 1.9), when controlling for age, education, ethnicity, marital status, smoking and gestational stage at study entry and consistent for all ethnic groups. However, during the third trimester, anemia was no longer a risk factor for preterm delivery.

The relationship between maternal hematocrit and preterm delivery in >17,000 women receiving iron and folate supplementation in Birmingham, Alabama was reported by Lu et al. (1991). Before midpregnancy, hematocrit (<37%) was weakly associated with an increased risk of preterm delivery. This finding, however, was not supported by multivariate analysis controlling for other risk factors. Hematocrits ≥40% before 20

[1] Presented at the symposium entitled "Improving Adolescent Iron Status before Childbearing" as part of the Experimental Biology 99 meeting held April 17–21 in Washington, DC. This symposium was sponsored by the American Society for Nutritional Sciences and was supported in part by an educational grant from Micronutrient Initiative. The proceedings of this symposium are published as a supplement to *The Journal of Nutrition*. Guest editors for the symposium publication were Kathleen Kurz, International Center for Research on Women and Rae Galloway, World Bank/Micronutrient Initiative.

[2] Supported by grants HD18269 and ES 07437 from the National Institutes of Health.

[3] To whom correspondence should be addressed.

wk, and between 31 and 34 wk gestation were significantly associated with an increased risk for preterm delivery. Preterm delivery was significantly associated with hematocrits ≥43% at 31–34 wk gestation (odds ratio > 2).

The above studies evaluated maternal hemoglobin concentrations and hematocrits as the sole indicators assessing iron status during pregnancy. In an effort to distinguish between iron deficiency anemia and anemias from other causes (e.g., inflammation, infection or hemodilution) and the risk for preterm delivery, Scholl et al. (1992) reported on 755 pregnant women receiving initial antenatal care at 16.7 ± 5.4 wk gestation in Camden, New Jersey. These investigators utilized serum ferritin concentrations (<12.0 μg/L) to characterize iron deficiency anemia because anemias from other causes are not associated with low ferritin concentrations (Institute of Medicine 1990). After controlling for confounding variables, women with iron deficiency anemia early in gestation had more than a twofold risk for preterm delivery (adjusted odds ratio = 2.66), whereas anemias from other causes were not associated with any increased risk for preterm delivery.

Previous or current vaginal bleeding at the time of the first antenatal care visit was documented in 18% of women with anemia. When vaginal bleeding occurred, risk of preterm delivery was increased fivefold when iron deficiency was present, and more than twofold when the anemia was the result of other causes. This finding suggested the possibility that fetal or maternal pathologies influenced the increased risk of preterm delivery and the vaginal bleeding, which contributed subsequently to the anemia.

In a follow-up study of this population at 28 wk gestation, Scholl and Hediger (1994) demonstrated that the risk was no longer increased for women who had iron deficiency anemia (15.6%) at this time or anemia from other causes. Although risk for preterm delivery was increased when iron deficiency anemia occurs early in gestation, iron deficiency later in pregnancy probably reflects mainly normal physiologicl expansion of maternal plasma volume.

These findings were supported by Zhou et al. (1998) who described the relationship of maternal hemoglobin concentrations during the first trimester and poor pregnancy outcome in 829 Shanghai women. In this population, other risk factors associated with poor pregnancy outcome (e.g., smoking or drinking) were uncommon and women enrolled for care early in the first trimester. Preterm delivery was associated with early pregnancy hemoglobin concentrations in a U-shaped relationship. The risk of preterm delivery was increased 1.6 times for women with hemoglobin concentrations between 100 and 109 g/L. A 2.6-fold increase in risk was noted for hemoglobin concentrations ranging from 90 to 99 g/L. The risk for preterm delivery increased 3.7-fold for hemoglobin concentrations between 60 and 89 g/L. When hemoglobin concentrations during mo 5 or 8 of gestation were considered, the risk for preterm delivery was greatly reduced.

Maternal anemia during gestation and poor pregnancy outcome

Associations between low maternal hemoglobin concentrations and hematocrits at delivery and poor pregnancy outcome have been reported in several studies. Garn et al. (1981) reported the effects of maternal anemia on pregnancy in >50,000 pregnancies. Although statistically significant, the relative risk for preterm delivery with low hematocrit (<29% at any gestation) was modest (≤1.5), except above 25%, where risk of preterm delivery was doubled for white, but not African-American women. These data, which were among the first to shed light on anemia and adverse pregnancy outcome, are compromised by failure to control for confounding variables (stage of gestation and hemodilution) known to influence the interpretation of hematologic measurements during gestation.

Using data from >35,000 pregnancies followed in the Collaborative Perinatal Project (CPP), Klebanoff et al. (1989) concluded that the relationship between maternal anemia at the time of delivery and preterm delivery was an artifact of blood sample collection time. During pregnancy, the normal physiologic changes in plasma volume and red cell mass occur at different periods during gestation. Because these changes are asynchronous, lower hematocrits typify earlier stages of pregnancy when preterm delivery commonly occurs, and higher hematocrit values are associated with pregnancies delivered at later gestational periods. This report did demonstrate a weak association between anemia early in the third trimester and preterm delivery. After 30 wk, anemia was not associated with an increased risk of preterm delivery.

High hemoglobin, ferritin and poor pregnancy outcome

Garn et al. (1981) reported hematologic data from the CPP, suggesting that fetal death, preterm delivery and low birth weight all were increased when the lowest values obtained during pregnancy exceeded 39% for hematocrit or 130 g/L for hemoglobin. Steer et al. (1995) confirmed the association, showing that failure of hemoglobin to fall below 105 g/L was associated with up to a sevenfold increase in risk of low birth weight and fivefold increase in risk of preterm delivery.

Other findings with high maternal hemoglobin have been observed early in pregnancy, as well as during the third trimester. Murphy et al. (1986) found that at every gestational stage examined, high hemoglobin (>133 g/L)was associated with increased risk of one or more poor outcomes. High booking hemoglobin was associated positively with maternal hypertension, a relationship that was evidenced as early as the first trimester. In general, most associations tended to be stronger later in pregnancy than in the first trimester, implicating plasma volume expansion.

Zhou et al. (1998) examined high hemoglobin along with anemia in their observational study. At entry to care, which ranged between 6 and 8.4 wk gestation, women with hemoglobin levels exceeding 130g/L had a greater than twofold increase in risk of preterm delivery and infant low birth weight. Neither risk was statistically significant, however, because of the small numbers with high hemoglobin.

Similarly, a concentration of the iron storage protein, ferritin, that is high for the third trimester of pregnancy is also associated with an increased risk for preterm and very preterm delivery. From their studies of Alabama women, both Tamura et al. (1996) and Goldenberg et al. (1996) found high third-trimester ferritin levels (>40 ng/L) to be a marker for an increased risk for preterm and very preterm delivery. Prospective data from Camden (Scholl 1998) indicated that high ferritin levels (>41.5 ng/L) during the third trimester, stemming from the failure of ferritin to decline from entry, increased risk of very preterm delivery more than eightfold. High ferritin also was associated with indicators of infection, including clinical chorioamnionitis (Scholl 1998) and infant sepsis among women with pregnancies complicated by premature rupture of membranes (Goldenberg et al. 1998). A hallmark of maternal hypovolemia, i.e., high maternal hemoglobin (>120 g/L), was more frequent among women with high ferritin (Scholl 1999) during the latter half of pregnancy. Thus, like hemoglobin, failure of the plasma volume to expand or hypo-

volemia also is implicated in the etiology of high maternal ferritin.

It is possible that anemia or other factors related to maternal nutritional status early in pregnancy are associated with later hypovolemia. Poorly nourished animals have reduced maternal plasma volume expansion during pregnancy and low cardiac output, with lower uteroplacental blood flow and nutrient transmission to the fetus (Rosso and Salas 1994). Similarly, Camden women with high third trimester ferritin had numerous indicators of poor nutritional status earlier in pregnancy [risk of anemia and iron deficiency anemia were increased, circulating levels of ferritin and serum and red cell folate were lower (Scholl 1998)]. Later on (wk 28), their profiles suggested hypovolemia, i.e., high hemoglobin was more frequent and anemia and iron deficiency anemia were less common than in controls (Scholl 1999).

Iron supplementation and pregnancy outcome

Controlled trials of iron supplementation during pregnancy have consistently demonstrated positive effects on maternal iron status at delivery. The prevalence of low hemoglobin or hematocrit is reduced; serum ferritin, serum iron and almost every other measure of maternal iron status, including bone marrow iron, are increased in comparison with controls (Mohamed 1998). However, the same benefits are not readily demonstrable when iron supplementation is incorporated into routine prenatal care. The estimated prevalence of third-trimester anemia that would occur in the absence of iron supplementation is estimated at 40%, compared with the 37% reported by the Centers for Disease Control (CDC) surveillance of low income women (Perry et al. 1995, Yip 1996).

Controlled trials of iron supplementation have not demonstrated reductions in factors that are associated with maternal anemia, i.e., increased risk of preterm delivery and infant low birth weight. However, effects on pregnancy outcome have been difficult to evaluate because few studies have addressed the effect of iron supplementation in groups in which anemia and iron deficiency anemia are prevalent (Mohamed 1998). In one meta-analysis examining differences in infant birth weight and morbidity in trials from Western Europe, five of six trials excluded women with low hemoglobin (<100g/L) at entry, women already taking iron supplements (who were likely to be iron deficient) and those with a prior poor pregnancy outcome. In three of six trials, patients with characteristics related to the outcome of interest (e.g., gravidas developing anemia or delivering preterm) were excluded (Hemminiki and Starfield 1978).

The trial of routine vs. selective iron supplementation (Hemminiki and Rimpela 1991a and 1991b) also focused on nonanemic women (hemoglobin >100 g/L at entry). Routine supplementation resulted in a reduced risk of infant low birth weight (odds ratio = 0.89) and preterm delivery (odds ratio = 0.71), which were not significant (Hemminiki and Rimpela 1991a and 1991b, Mohamed 1998, Mohamed and Hytten 1989). Thus, although the conclusion that iron supplementation has no effect on the outcome of pregnancy may be true, its efficacy has been evaluated almost exclusively among women who were not anemic early in pregnancy and were therefore less likely to realize the potential benefits of supplementation.

Some trials conducted among women from the developing world, in which anemia and presumably iron deficiency are prevalent, have come to somewhat different conclusions albeit from smaller numbers and often with substantial loss to follow-up and potential bias to the results of the trial. Preziosi et al. (1997), for example, supplemented Nigerian women with elemental iron (100 mg) during the third trimester and found improvements in indices of maternal iron status, birth length and Apgar scores but no difference in infant birth weight. Agarwal et al. (1991) randomized women from six subcenters in an Indian district to iron/folate (60 mg elemental iron + 500 μg folic acid) or placebo. After excluding preterm deliveries, they reported improvements in infant birth weight and term low birth weight with supplementation.

Adverse effects of iron supplementation

One concern voiced about iron supplementation during pregnancy is that because iron allays the fall in hemoglobin during pregnancy, iron-induced macrocytosis could increase blood viscosity to a degree that would impair uteroplacental blood flow, decrease placental perfusion and increase risk of placental infarction (Koller 1982, Mohamed and Hytten 1989).

Hemminiki and Rimpela (1991a and 1991b) conducted a clinical trial of selective vs. routine iron supplementation in 2912 Finnish women. Data from that multicenter study were examined to determine whether routine supplementation with iron in nonanemic women increased risk of high maternal hemoglobin and poor fetal growth. Women randomized to the selective iron group received iron supplements only when hematocrit fell below 30% or hemoglobin below 100 g/L on two consecutive visits after week 33.

Routine supplementation with iron did increase maternal hematocrit. In selectively supplemented women, hematocrit declined from wk 12 to 28, whereas in routinely supplemented women, the decline was arrested by wk 20. Although routine supplementation increased hematocrit, it did not alter infant birth weight. In contrast, gestation duration was increased significantly (+ 0.2 wk). Interestingly, in both routine and selectively supplemented groups, hematocrit was negatively correlated with birth weight and placental weight. This correlation was first evidenced at baseline (i.e., wk 12 gestation) and persisted after adjusting for the effect of maternal blood pressure. Thus, rather than iron supplementation, factors that are intrinsic to pregnancy (poor plasma volume expansion, increased blood viscosity) and that are evidenced early in gestation seem to link high hemoglobin with poor pregnancy outcome.

Scholl (1999) and Scholl and Schroeder (1999) examined the influence of elemental iron supplement use on high third-trimester ferritin levels and risk of preterm and very preterm delivery. Both anemic and nonanemic gravidas who used elemental iron supplements by wk 28 were compared with gravidas without such supplement use. Anemia was assessed at entry to care (15 ± 4.9 wk) by hemoglobin concentration using the CDC criteria for pregnancy (Centers for Disease Control and Prevention 1989).

After control for potential confounding variables and in comparison to gravidas who did not use iron, anemic women had a significantly (>threefold) increased risk of high ferritin at wk 28 when they used iron. Nonanemic women who used iron also sustained a significant increase in the odds of a high ferritin level; in this case, risk was increased twofold in comparison to controls (**Table 1**). Interestingly, the absolute risk of having a high third-trimester ferritin level was greater among the anemic than among nonanemic women using iron (Table 1). Consistent with the findings of Hemminiki and Rimpela (1991a and 1991b) on iron supplementation and

TABLE 1

Iron supplement use during pregnancy and high serum ferritin and very preterm and preterm delivery

		High 3rd trimester ferritin[1,2]			Very preterm delivery[3,4]			Preterm delivery[4,5]		
Iron use	*n*	%[6]	AOR	95% CI	%[6]	AOR	95% CI	%[6]	AOR	95% CI
Anemic[7]	140	23.6	3.01	1.82–4.99	7.1	1.25	0.55–2.82	22.1	1.37	0.84–2.10
Not anemic	249	13.6	2.05	1.27–3.30	4.0	0.77	0.35–1.68	13.7	0.91	0.58–1.44
No iron use	620	8.2	1.00	—	4.0	1.00	—	13.7	1.00	—

[1] Ferritin $>$ 41.5 μg/L.
[2] Adjusted for age, parity, ethnicity, cigarettes/d and gestation at blood draw.
[3] Less than 33 completed weeks gestation.
[4] Adjusted for age, parity, ethnicity, cigarettes/d, inadequate weight gain, pregravid body mass index, prior preterm delivery and gestation at blood draw.
[5] Less than 37 completed weeks gestation.
[6] Unadjusted proportion with high ferritin ($\geq$41.5 μg/L), very preterm or preterm delivery.
[7] At entry to care (15.0 $\pm$ 4.9 wk gestation) by Centers for Disease Control (1989) criteria for hemoglobin.
AOR, adjusted odds ratio; CI, confidence interval.

birth weight, elemental iron use did not increase risk of preterm or very preterm delivery in either anemic or nonanemic gravidas (Table 1).

Another current concern is that iron supplements are a possible source of free radical development with the potential to cause oxidative damage to DNA, lipids and protein (Knutson et al. 1999, Lund et al. 1999). Apart from the association of preeclampsia with oxidative stress (Walsh 1998), this is an area that has been little explored during pregnancy. Oxidative stress is believed to be involved in the etiology of cardiovascular disease, cancer, cataracts, inflammatory diseases, immune function and numerous other disorders (Gutteridge and Halliwell 1994). During pregnancy, oxidative stress from iron supplementation has the potential to damage the conceptus, increasing risk of congenital defects, preterm delivery and low birth weight in the short term.

Clearly many issues surrounding iron supplementation during pregnancy must be addressed, including the appropriate window in which supplements may have maximum effect on the associated risks and compliance with the use of iron supplements. Assessing deficits in iron stores also would be important for identifying women who are iron deficient and most likely to be responsive to iron supplementation. If anemia is in fact due to iron deficiency and is causally related to preterm delivery, then iron supplementation in the appropriate window should reduce that risk. Viteri (1997) suggests providing menstruating women at risk with weekly iron/folate tablets, an intervention likely to improve a women's iron status before conception and reduce the risk of iron deficiency anemia in early pregnancy.

Apart from a few trials in the developing world in which loss to follow-up is problematic, questions about the efficacy and hypothetical side effects of iron supplementation (e.g., greater oxidative stress or impaired utero-placental blood flow) have not been addressed with the use of a randomized, double-blind design in an appropriate population. Such a population is one in which anemic women are likely to be iron deficient, one in which iron supplementation is not the norm because of ethical considerations about withholding treatment, and one in which women can be followed and monitored until they deliver because of the potential bias and misinterpretation associated with substantial loss to follow-up.

LITERATURE CITED

Agarwal, K. N., Agarwal, D. K. & Mishra, K. P. (1991) Impact of anaemia prophylaxis in pregnancy on maternal haemoglobin, serum ferritin and birth weight. Indian J. Med. Res. 94: 277–280.

Centers for Disease Control and Prevention (1989) CDC criteria for anemia in children and childbearing-aged women. Morb. Mortal. Wkly. Rep. 38: 400–404.

Garn, S. M., Ridella, S. A., Petzoid, A. S. & Falkner, F. (1981) Maternal hematologic levels and pregnancy outcomes. Semin. Perinatol. 5: 155–162.

Goldenberg, R. L., Mercer, B. M., Miodovnik, M., Thurnau, G. R., Meis, P. J., Moawad, A., Paul, R. H., Bottoms, S. F., Das, A., Roberts, J. M., McNellis, D. & Tamura, T. (1998) Plasma ferritin, premature rupture of membranes, and pregnancy outcome. Am. J. Obstet. Gynecol. 179: 1599–1604.

Goldenberg, R. L., Tamura, T., DuBard, M., Johnston, K. E., Copper, R. L. & Neggers, Y. (1996) Plasma ferritin and pregnancy outcome. Am. J. Obstet. Gynecol. 175: 1356–1359.

Gutteridge, J.M.C. & Halliwell, B. (1994) Antioxidants in Nutrition, Health and Disease. Oxford University Press, New York, NY.

Hemminki, E. & Rimpela, U. (1991a) Iron supplementation, maternal packed cell volume, and fetal growth. Arch. Dis. Child. 66: 422–425.

Hemminki, E. & Rimpela, U. (1991b) A randomized comparison of routine versus selective iron supplementation during pregnancy. J. Am. Coll. Nutr. 10: 3–10.

Hemminiki, E. & Starfield, B. (1978) Routine administration of iron and vitamins during pregnancy: review of controlled clinical trials. Br. J. Obstet. Gynaecol. 85: 404–410.

Institute of Medicine, Committee on Nutritional Status during Pregnancy and Lactation (1990) Nutrition during Pregnancy, pp. 272–298. National Academy Press, Washington, DC.

Klebanoff, M. A., Shiono, P. H., Berendes, H. W. & Rhoads, G. G. (1989) Facts and artifacts about anemia and preterm delivery. J. Am. Med. Assoc. 262: 511–515.

Klebanoff, M. A., Shiono, P. H., Selby, J. V., Trachtenberg, A. I. & Graubard, B. I. (1991) Anemia and spontaneous preterm birth. Am. J. Obstet. Gynecol. 164: 59–63.

Knutson, M. D., Walter, P. B., Mendoza, C., Ames, B. N. & Viteri, F. E. (1999) Effects of daily and weekly oral iron supplements on iron status and lipid peroxidation in women. FASEB J. 13: 536–537.

Koller, O. (1982) The clinical significance of hemodilution during pregnancy. Obstet. Gynecol. Surv. 37: 649–652.

Lu, Z. M., Goldenberg, R. L., Cliver, S. P., Cutter, G. & Blankson, M. (1991) The relationship between maternal hematocrit and pregnancy outcome. Obstet. Gynecol. 77: 190–193.

Lund, E. K., Wharf, S. G., Fairweather-Tait, S. J. & Johnson, I. T. (1999) Oral ferrous sulfate supplements increase the free radical-generating capacity of feces from healthy volunteers. Am. J. Clin. Nutr. 69: 250–255.

Mohamed, K. (1998) Routine iron supplementation during pregnancy (Cochrane Review) In: The Cochrane Library, issue 3, Update Software. Oxford, UK.

Mohamed, K. & Hytten, F. (1989) Iron and folate supplementation in pregnancy. In: Chalmers, I., Enkin, M., Keirse, MLJC (eds), Oxford Unviersity Press, Oxford, UK pp 301–317.

Murphy, J. F., O'Riordan, J., Newcombe, R. G., Coles, E. C. & Pearson, J. F. (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. Lancet 1: 992–995.

Perry, G. S., Yip, R. & Zyrkowski, C. (1995) Nutritional risk factors among low-income pregnant US women: the Centers for Disease Control and Pre-

vention (CDC) pregnancy nutrition surveillance system, 1979 through 1993. Semin. Perinatol. 19: 211–221.
Preziosi, P., Prual, A., Galan, P., Daouda, H., Boureima, H. & Hercberg, S. (1997) Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. Am. J. Clin. Nutr. 66: 1178–1182.
Rosso, P. & Salas, S. P. (1994) Mechanisms of fetal growth retardation in the underweight mother. Adv. Exp. Biol. Med. 352: 1–9.
Scholl, T. O. (1998) High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. Obstet. Gynecol. 92: 161–165.
Scholl, T. O. (1999) High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. Obstet. Gynecol. 93: 156–157.
Scholl, T. O. & Hediger, M. L. (1994) Anemia and iron deficiency anemia: compilation of data on pregnancy outcome. Am. J. Clin. Nutr. 59: 492S–501S.
Scholl, T. O., Hediger, M. L., Fischer, R. L. & Shearer, J. W. (1992) Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. Am. J. Clin. Nutr. 55: 985–988.
Scholl, T. O. & Schroeder, C. M. (1999) High ferritin and very preterm delivery: influence of iron supplements during pregnancy Ann. Behav. Med. 21: S087.
Steer, P., Alam, M. A., Wadsworth J. & Welch, A. (1995) Relationship between maternal haemoglobin concentration and birth weight in different ethnic groups. Br. Med. J. 310: 489–491.
Tamura, T., Goldenberg, R. L., Johnston, K. E., Cliver, S. P. & Hickey, C. A. (1996) Serum ferritin: a predictor of early spontaneous preterm delivery. Obstet. Gynecol. 87: 360–365.
Viteri, F. E. (1997) Effective iron supplementation does not happen in isolation (letter). Am. J. Clin. Nutr. 65: 889–890.
Walsh, S. W. (1998) Maternal-placental interactions of oxidative stress and antioxidants in pre-eclampsia. Semin. Reprod. Endocrinol. 6: 93–104.
Yip, R. (1996) Iron supplementation during pregnancy: is it effective? Am. J. Clin. Nutr. 63: 853–855.
Zhou, L. M., Yang, W. W., Hua, J. Z., Deng, C. Q., Tao, X. & Stolzfus, R. J. (1998) Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. Am. J. Epidemiol. 148: 998-1006.