22. Screening for Iron Deficiency Anemia—*Including Iron Prophylaxis*

RECOMMENDATION

Screening for iron deficiency anemia using hemoglobin or hematocrit is recommended for pregnant women and for high-risk infants. There is insufficient evidence to recommend for or against routine screening for iron deficiency anemia in other asymptomatic persons, but recommendations against screening may be made on other grounds (see ***Clinical Intervention***). Encouraging parents to breastfeed their infants and to include iron-enriched foods in the diet of infants and young children is recommended (see also Chapter 56). There is currently insufficient evidence to recommend for or against the routine use of iron supplements for healthy infants or pregnant women.

Burden of Suffering

Anemia is defined by the presence of a hemoglobin level that is below the normal range of values for the population (see *Accuracy of Screening Tests*).[1–4] U.S. populations with a high prevalence of anemia include blacks, Alaska Natives and Native Americans, immigrants from developing countries, and individuals of low socioeconomic status.[5–7] Anemia may be due to a variety of underlying conditions. Iron deficiency is an important cause among young children and women of reproductive age in the U.S.[8–10] The prevalence of iron deficiency anemia in U.S. children has declined in recent years[6,11–14] and in 1993 was estimated to be at or below 3% for children aged 1–5.[15] In low-income populations and certain ethnic groups, such as Alaska Natives, the prevalence of iron deficiency anemia in children <5 years of age may be substantially higher, ranging from 10–30% (unpublished data, Centers for Disease Control and Prevention, 1993).[6] Among middle-class children, on the other hand, anemia is uncommon and tends to be mild (i.e., within 1% of the hematocrit level defining anemia).[13,14] The exact prevalence of iron deficiency anemia among pregnant women is uncertain, but national data suggest that <2% of nonpregnant

women aged 20–44 years have iron deficiency anemia.[5] Among low-income, pregnant U.S. populations, a low hemoglobin level and/or low hematocrit is present in 6% of white women and 17% of black women during the first trimester and in 25% of white women and 46% of black women during the third trimester.[7] The high rates of anemia in pregnant women may not be attributable to iron deficiency, however. In a large cohort of urban, low-income, mostly minority pregnant women, only 12.5% of anemic women were iron deficient.[16]

As early as the 1960s, researchers demonstrated that, in general, decreased hemoglobin alone does not have readily apparent adverse effects unless it is below 10 g/dL (100 g/L).[17–19] Clearly, persons with markedly reduced hemoglobin levels are at risk for cardiopulmonary and other complications. Reduced work productivity, endurance, and exercise capacity have been associated with anemia or iron deficiency anemia in adults, most of whom were from developing countries.[20–26] Iron deficiency and iron deficiency anemia during infancy and early childhood have been associated with abnormal infant behavior, growth, and development, although it is unclear how much of this association is actually attributable to other factors often associated with iron deficiency (e.g., poor nutrition, low socioeconomic status).[27–35] Hemoglobin levels well below what is considered normal for pregnancy have been associated with increased risk of low birth weight, preterm delivery, and perinatal mortality.[16,36–42]

Accuracy of Screening Tests

The hemoglobin concentration and hematocrit are the principal screening tests for detecting anemia. The World Health Organization hemoglobin cut-points for diagnosing anemia in adults have been widely adopted: men, <13 g/dL; menstruating women, <12 g/dL; pregnant women, <11 g/dL.[1] The Centers for Disease Control and Prevention (CDC) has also produced criteria for anemia: in infancy and childhood, <11 g/dL for 0.5–4.9 years and <11.5 mg/dL for 5.0–11.9 years; in pregnancy, <11 g/dL during the first and third trimesters and <10.5 g/dL in the second trimester.[2] Studies have shown that automated electronic cell counters and chemical analyzers provide accurate and reliable data on red blood cell number and size and on the concentration of hemoglobin.[43,44] Although sampling of capillary blood is more convenient in ambulatory practice and is especially useful for infant testing, results obtained from capillary blood specimens are less reliable than those from venous blood.[45,46] One study found the capillary microhematocrit to have a sensitivity of 90% and a specificity of 44% when compared with values obtained from venous blood with an automated cell counter.[46]

While sensitive for iron deficiency anemia, hemoglobin is not sensitive

for iron deficiency because mild deficiency states may not affect hemoglobin levels.[47] Hemoglobin is also nonspecific, since many cases of anemia are due to causes other than iron deficiency.[9,10,16] Reported sensitivity of low hemoglobin for detecting iron deficiency ranges from 8–90% and specificity from 65–99% depending on the population, reference standard and cut-point used.[47–50] In a national sample, detection of a hemoglobin <12 g/dL had a sensitivity of 90% and specificity of 78% for iron deficiency in black women, whereas sensitivity and specificity were 36% and 95% in white women.[50] Other tests (i.e., total iron binding capacity, serum iron, transferrin saturation, erythrocyte protoporphyrin, mean cell volume, red blood cell distribution width, and serum ferritin) may be more accurate for the detection of iron deficiency, but they are poor screening tests for iron deficiency anemia.[48,51–59] Among these tests, serum ferritin has the best sensitivity and specificity for diagnosing iron deficiency in anemic patients.[60]

Effectiveness of Early Detection

Evidence is limited that in the asymptomatic general adolescent or adult U.S. population, early detection and treatment significantly reduces morbidity from anemia, iron deficiency, or the conditions that cause them.[17–19,61] This evidence is further limited by the fact that studies often use inconsistent or vague definitions of anemia and iron deficiency. Observational studies in developing countries have reported decreased physical endurance and maximal exercise capacity in association with iron deficiency anemia.[21–24,26] The extent to which this might affect daily activities that do not involve maximal exercise capacity is unknown. Clinical trials and case series from developing countries have reported conflicting results regarding a benefit of iron supplementation on work productivity in anemic or iron-deficient workers.[22,25,62–64] There is little evidence evaluating adverse effects from the mild degree of anemia that is most often detected by screening asymptomatic persons in developed countries. In a Swedish cohort, anemic women (Hgb <12 g/dL) reported no increase in reported infections, fatigue, or other symptoms, but they were significantly more likely to report low work productivity compared to nonanemic women.[20] In a small, randomized placebo-controlled trial of Welsh women with anemia (hemoglobin <10.5 g/dL) detected by population-based screening, iron therapy did not result in clinically or statistically significant improvements in psychomotor function tests, symptoms, or subjective well-being, despite increased hemoglobin concentrations.[65] Trials evaluating the effects of iron supplementation on physiologic outcomes such as running speed and maximum running time in nonanemic, iron-depleted runners have been inconclusive.[66,67] Although the evaluation of anemia may

disclose underlying diseases (e.g., occult malignancies) that benefit from early detection,[68] there are no data to suggest that testing for anemia is an effective means of screening for these conditions.

A number of trials have evaluated whether infants with iron deficiency anemia benefit from early treatment. Randomized controlled trials have demonstrated the efficacy of iron supplementation in correcting iron deficiency anemia in infants and children, but its effect on clinical outcomes is less clear.[27,28,69,70] Four relatively large, generally well-conducted, randomized controlled trials in developing countries have evaluated the effects of iron supplementation on the behavior and development of anemic infants.[27,28,31,70] Three trials failed to show a significant effect of treatment on standardized developmental test scores after short-term (6–10 days) iron therapy.[27,28,31] In one trial,[31] an additional 3 months of iron therapy for all infants corrected their anemia but did not significantly improve developmental test scores. Another of the trials[27] reported that after 3 months of iron therapy infants whose iron deficiency was completely corrected (36%) had developmental scores similar to iron sufficient subjects, mainly because the scores of the latter group declined. In the remaining 64%, treatment corrected anemia but not iron deficiency, and test scores remained lower in this group. This trial did not have a true placebo group, and other causes of anemia (such as vitamin A deficiency) were not adequately excluded. There was no delayed benefit of iron therapy in this trial; children with hemoglobin ≤10 g/dL as infants still had lower developmental scores at school entry 5 years later.[33] The largest and most recent trial, which enrolled 12–18-month-old infants with hemoglobins ≤ 10.5 g/dL, reported sizable, statistically significant improvements in both mental and motor development after 4 months of oral therapy.[70] A small randomized double-blind placebo-controlled trial[71] in the United Kingdom evaluated 2 months of iron supplementation in urban, underprivileged toddlers (aged 17–19 months) with mild to moderate anemia, using the Denver developmental screening test to assess outcome, which is not as well standardized or validated as the test used in the other trials. Effects on developmental outcomes were inconsistent, but iron supplements significantly increased rate of weight gain. Long-term results were not evaluated. It is unclear why the results of these trials differ, although adequacy and duration of therapy may account for some of the differences.

Clinical trials and a cohort study in older children have also demonstrated improved iron and hemoglobin status with therapy,[35,69,72] but evidence for a clinical benefit from treatment of iron deficiency anemia is limited. A double-blind randomized controlled trial in 1,358 9–11-year-old Thai children failed to show any effect of iron treatment on intelligence test scores in anemic children, despite the large sample size.[73] A series of small randomized controlled trials conducted in India did report small im-

provements in IQ with iron treatment,[74,75] however, and two small randomized, controlled trials suggested a benefit of oral iron on some tests of learning in anemic school-aged Indonesian children.[76,77] All of these studies suffered from important design limitations, such as use of unvalidated tests, multiple significance testing, high dropout rates, and addition of folic acid to the treatment regimen. Conflicting results have been reported concerning the effect of iron supplementation on infection rates in children.[35,78–80] On the other hand, improved growth and weight gain with 3–6 months of iron supplementation have been reported consistently in placebo-controlled trials of anemic, malnourished children in developing countries.[34,35,81,82] Another controlled trial reported a significant benefit from iron treatment on physical performance and submaximal work capacity in anemic Indian boys.[83] It is unclear whether the results of these studies are generalizable to U.S. children, who are likely to be healthy and otherwise adequately nourished.

Early detection and treatment of iron deficiency anemia in pregnancy has been assumed to be beneficial because moderate to severe anemia (i.e., <9.0–10.0 g/dL) has been associated with a 2–3-fold increased risk of low birth weight, preterm delivery, and perinatal mortality in numerous cross-sectional and longitudinal observational studies in industrialized countries.[16,36–42,84] The consistency of these results across different study designs and population samples is noteworthy, although such studies do not conclusively prove that anemia directly influences pregnancy outcomes. Many of the studies did not control for other factors that may have had adverse effects (e.g., smoking, maternal malnutrition), or for increases in hemoglobin and hematocrit that occur as gestation approaches term; most did not differentiate iron deficiency anemia from anemia due to other causes. A large body of data suggests that iron supplements are effective in improving the hematologic indices of pregnant women,[85–91] but there is limited evidence that improving hematologic indices in anemic women results in improved clinical outcomes for the mother, fetus, or newborn. Most published trials evaluating the effects of iron supplementation on pregnancy outcomes systematically excluded anemic women (i.e., those with hemoglobins <10 g/dL or hematocrits ≤0.3) and are therefore not necessarily relevant to pregnant women with iron deficiency anemia. They are described later in the chapter (see *Primary Prevention*). One controlled trial enrolled Indian women with hemoglobins as low as 7.0 g/dL who attended rural health centers, randomizing the women by health center to receive either iron and folic acid supplements for 100 days or no supplements.[92] The trial reported a significantly higher mean birth weight and lower rate of low birth weight infants in women who completed 100 days of supplements compared to controls. Among those receiving supplementation, the increase in birth weight was significantly related to

rise in hemoglobin. A large (n = 601), retrospective cohort study from Kenya compared women with severe anemia (hemoglobin ≤8.8 g/dL) who were or were not treated with ferrous sulfate.[93] Treatment was associated with markedly reduced preterm delivery and stillbirth rates, and increased mean birth weight, but there was no change in neonatal death rates. Women with "mild anemia" (hemoglobin ≥8.9 g/dL) who received iron therapy before 30 weeks also had lower preterm delivery and perinatal mortality rates compared to those receiving no iron or iron after 30 weeks. Neither significance testing nor adjustment for covariates was performed, limiting the conclusions that can be drawn from these data. The detection of anemia and the determination of its etiology may also lead to the discovery of other correctable obstetrical risks (e.g., poor nutritional status, medical illness) that might otherwise escape detection, but the effectiveness of anemia screening in improving outcomes related to these risks has not specifically been evaluated in developed countries.

Adverse effects of iron therapy include unpleasant gastrointestinal symptoms (e.g., nausea and constipation) that are dose-related and, at normal doses, reversible.[94–97] Iron therapy can cause complications of excessive iron storage in patients with an underlying iron storage disorder (e.g., idiopathic hemochromatosis).[98,99] A potential hazard of iron supplements is unintentional overdosage by children in the home; 20,330 cases of ingestion of iron or iron-containing vitamins by children under 6 years, including 3 fatalities, were reported to poison control centers in 1993.[100] Iron supplements accounted for 30% of fatal pediatric pharmaceutical overdoses occurring between 1983 and 1990.[101] Other potential adverse effects of iron mentioned in the literature (e.g., birth defects, cancer, heart disease, infection, metabolic imbalances of other minerals, and harmfully high hemoglobin levels)[109] have not been proven.

Primary Prevention (Iron Prophylaxis)

Studies of the effects of iron fortification of formula and cereal on healthy, nonanemic infants have focused primarily on laboratory rather than clinical outcomes. Randomized and nonrandomized controlled trials, observational studies, and time series studies have demonstrated substantial reductions in the incidence of iron deficiency and iron deficiency anemia in healthy infants fed iron-fortified formula, iron-fortified cereal, or breast milk (with iron-fortified cereal added at 4–6 months), compared to infants fed cow's milk or unfortified formula.[12,102–107] Evidence is more limited regarding clinical benefits from iron fortification of infant diets. A cohort study reported that infants fed iron-fortified formula beginning at age 6 months had significantly fewer diarrheal episodes compared to infants fed whole cow's milk (0.16 vs. 0.30 per child in the second 6 months of life);

the incidence of other medical conditions (e.g., otitis media, dermatitis, wheezing) did not differ.[106] This study did not have standardized criteria for diagnosing medical conditions and had limited control for potentially confounding variables, however. A controlled trial randomized healthy infants at a mean age of 1.3 months to either iron-fortified or nonfortified milk-based formula.[108] Infants in the fortified group had a significantly greater height (by 0.9 cm) and growth rate at 12 months, but this group was also significantly taller at birth. At 12 months, there were no other statistically significant differences in clinical outcomes, such as weight, number of acute illnesses, or psychomotor development. Intake of the iron-fortified formula may have been insufficient to produce a clinical effect, however; by 8 months of age, 92% of study infants and 85% of controls were drinking cow's milk rather than study formula. In another randomized controlled trial in healthy infants from very low income families, infants randomized to nonfortified formula had significantly worse psychomotor development (Bayley Scales) at 9 and 12 months of age compared to those given iron-fortified formula.[108a] Differences were no longer significant at 15 months, although sample size may have been inadequate: only half the sample was assessed at 15 months. There were no differences at any age in standardized tests of cognitive development or behavior. These results suggest a clinical benefit from iron-fortified formula, but further trials are needed to confirm these results and determine their long-term impact.

Evidence is limited that iron supplementation in healthy pregnant women with mild or no anemia results in important clinical benefits.[109] Clinical trials have reported that iron supplements in healthy pregnant women with initial hemoglobins ≥10 g/dL are efficacious in correcting red cell indices and iron stores, but they do not improve birth weight, length of gestation, or other outcome measures when compared to placebo or to no supplements.[110–116] Few of these trials had sufficient statistical power to detect small positive effects of iron supplementation, however. One small randomized controlled trial in young pregnant women suggested a modest beneficial effect of routine iron supplementation on some tests of psychomotor function, but it had important discrepancies in reported data and analyses.[118] In a large randomized controlled trial of healthy, nonanemic pregnant women, routine iron therapy was compared to selective iron therapy given only when a confirmed hemoglobin level below 10 g/dL was detected after 14 weeks.[119] Women in the selective group had poorer self-reported overall health and increased rates of transfusion and operative delivery, although differences were small and may have been due to nonblinding. The routine supplementation group had more subjective side effects attributable to iron, more postdate gestations, and higher perinatal mortality; the latter difference was probably attributable to chance, given

small numbers and multiple comparisons. Evidence thus does not confirm important clinical benefits from routine iron supplementation in nonanemic pregnant women.

Cohort studies have reported no important adverse effects with iron-fortified formula,[120,121] nor were serious side effects reported in the clinical trials of iron-fortified food or formula previously cited. Routine iron supplementation may produce mild, reversible gastrointestinal symptoms similar to those seen with iron therapy (see above). In one small, randomized controlled trial, oral iron supplements in iron-sufficient children resulted in significantly less weight gained after 4 months of treatment,[122] but additional studies are needed to confirm these results. Trials of routine iron supplementation in pregnancy have not reported adverse effects on pregnancy outcome. The doses of oral iron typically offered for routine iron supplementation (e.g., in pregnancy) are unlikely to cause complications of excessive iron storage.[98,99] As with iron therapy, an important hazard of iron prophylaxis is unintentional overdosage by children in the home; many reported cases of iron ingestion involve iron-containing prenatal vitamins.[100]

Recommendations of Other Groups

A number of organizations recommend some form of anemia screening during infancy and pregnancy. The Institute of Medicine (IOM), the Canadian Task Force on the Periodic Health Examination, and the Bright Futures report recommend screening high-risk infants (e.g., preterm or low birth weight, low socioeconomic status, those fed with cow's milk or nonfortified formula before 12 months of age) between 6 or 9 and 12 months of age; IOM recommends screening before 3 months in preterm infants.[15,123,124] The American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) recommend that all infants receive a hemoglobin or hematocrit measurement once during infancy; the AAP recommends that it be done at or before 9 months of age.[125,126] The recommendations of the AAFP are currently under review. Prenatal screening for anemia is recommended by the Canadian Task Force,[127] the American College of Obstetricians and Gynecologists (ACOG),[128] and the IOM.[15] ACOG recommends measuring a hemoglobin or hematocrit at the earliest prenatal visit and again early in the third trimester;[128] IOM recommends measuring hemoglobin once in each trimester.[15]

Routine screening of older children or nonpregnant adolescents and adults is not advocated by most organizations.[15,124,126,128,129] Some organizations recommend screening selectively in specific high-risk populations: adolescents at increased risk due to heavy menses, chronic weight loss, nu-

tritional deficit, or athletic activity;[124] recent immigrants from undeveloped countries;[129] the institutionalized elderly;[129] and nonpregnant women aged 15–25 or otherwise at increased risk (e.g., with large menstrual blood loss, high parity, poverty, recent immigration).[15] The AAP recommends at least one measurement of hemoglobin or hematocrit for all menstruating adolescents, preferably at age 15 years.[125]

Primary prevention of iron deficiency anemia in infancy by breastfeeding, feeding iron-fortified formula if not breastfeeding, and feeding iron-fortified cereal after 4–6 months of age, is recommended by the Canadian Task Force,[123] IOM,[15] AAP,[130,131] and Bright Futures.[124] The AAFP recommends counseling parents of children under 6 years of age and women of childbearing age on the benefits of iron-enriched food and iron intake.[126] The AAP recommends iron supplements in breastfed term infants who do not receive iron-fortified cereal beginning at 4 months of age.[131] The Canadian Task Force found insufficient evidence to recommend for or against the routine use of iron supplements in pregnant women.[123] The IOM does not recommend routine iron supplements in nonanemic pregnant women.[15] ACOG and AAP recommend dietary supplements including iron during pregnancy if dietary intake is inadequate to meet need, or if there are other risk factors for iron deficiency.[128]

Discussion

The burden of suffering from iron deficiency anemia in the general child, adolescent, and adult populations in the U.S. is low. Although it is prevalent in certain high-risk groups, mild iron deficiency anemia in the absence of symptoms appears to have only subtle health consequences in these individuals. Trials of iron therapy in school children, adolescents, and adults have not proven important clinical benefits in well-nourished populations in developed countries. Thus, there is little evidence to suggest that early detection of iron deficiency anemia in these groups is beneficial. Treatment of some forms of anemia not caused by iron deficiency (e.g., vitamin B_{12} or folate deficiency), and some medical disorders that cause anemia, which would also be detected if hemoglobin measurement was performed routinely, can produce dramatic results. These disorders are too rare in most subgroups of the population to justify mass screening, however. There is therefore little basis for large-scale efforts to screen for anemia in the general population.

There is fair evidence to support screening for anemia in pregnant women, based on numerous observational studies reporting an association between severe to moderate anemia (hemoglobin <9–10 g/dL) and poor

pregnancy outcome, and weak evidence from a nonrandomized controlled trial and a cohort study that iron treatment of anemic women improves obstetric outcomes. Women of low socioeconomic status and immigrants from developing countries, among whom iron deficiency anemia is more common, are most likely to benefit from such screening. Because hemoglobin measurement is a nonspecific test for iron deficiency, further evaluation should be performed to identify the etiology of anemia detected by screening. Serum ferritin appears to have the best sensitivity and specificity for diagnosing iron deficiency in anemic patients. Although routine iron supplementation improves hematologic indices and iron status, there is at present insufficient evidence from published clinical research to suggest that routine iron supplementation of healthy pregnant women with hemoglobins ≥10 g/dL is beneficial in improving clinical outcomes for the mother, fetus, or newborn.[109]

The prevalence of iron deficiency anemia in the general infant population is low, and when it occurs in low-risk populations, it tends to be mild. In healthy, low-risk populations, there are few observational data showing adverse effects of iron deficiency anemia, nor have there been trials of early detection and correction of iron deficiency anemia. There is therefore little evidence to support routine hemoglobin measurement in infancy for the detection of iron deficiency anemia. On the other hand, multiple observational studies in high-risk populations (i.e., low socioeconomic status or developing countries) have found an association between iron deficiency anemia in childhood and abnormal growth and development. The largest and most recent trial[70] of iron therapy in a high-risk population showed an important effect of iron therapy on development, while several trials in high-risk, often malnourished, infants and children have found beneficial effects of iron on growth and growth rates. In the U.S., certain infants (e.g., recent immigrants from developing countries, those of low socioeconomic status, members of certain minority and ethnic groups, preterm infants, those who begin cow's milk before 12 months) have a substantially higher prevalence of iron deficiency anemia and may also be more likely to suffer from general malnutrition. There is therefore fair evidence to support screening high-risk infants and toddlers for iron deficiency anemia, using hemoglobin (or hematocrit). As for pregnant women, evaluation to determine the etiology of anemia is appropriate. Both breastfeeding and eating iron-fortified formula and cereal are effective in the primary prevention of iron deficiency anemia. Given the absence of known adverse effects from such dietary interventions, and the other important benefits of breastfeeding (see Chapter 56), evidence supports encouraging mothers to breastfeed and to include iron-enriched foods in the diet of infants and young children.

CLINICAL INTERVENTION

A hemoglobin analysis or hematocrit is recommended for pregnant women at their first prenatal visit ("B" recommendation). There is insufficient evidence to recommend for or against repeated prenatal testing for anemia in asymptomatic pregnant women lacking evidence of medical or obstetrical complications ("C" recommendation). Screening for anemia with hemoglobin or hematocrit in high-risk infants, preferably at 6–12 months of age, is also recommended ("B" recommendation). Examples of high-risk infants include infants living in poverty, blacks, Native Americans and Alaska Natives, immigrants from developing countries, preterm and low birth weight infants, and infants whose principal dietary intake is unfortified cow's milk. Although capillary blood specimens are easier to obtain in infants, a venous blood count provides more accurate and reliable data. Serum ferritin testing may be useful as an additional screening test in selected high-risk infants. There is currently insufficient evidence to recommend for or against periodic screening for high-risk infants not found to be anemic at initial screening ("C" recommendation). There is also insufficient evidence to recommend for or against routine testing for anemia in other asymptomatic persons, but recommendations against such screening may be made on the grounds of low prevalence, cost, and potential adverse effects of iron therapy ("C" recommendation).

Guidelines for normal hemoglobin ranges for infants and pregnant women have been published.[1–4] Appropriate hematological studies and nutrition counseling should be provided for patients found to have anemia. Compared to other diagnostic tests, serum ferritin has the best sensitivity and specificity for detecting iron deficiency in patients found to be anemic. Screening for hemoglobinopathies is discussed in Chapter 43.

Encouraging mothers to breastfeed their infants and advising parents to include iron-enriched foods in the diet of infants and young children is recommended for the primary prevention of iron deficiency anemia ("B" recommendation). There is also good evidence to recommend breastfeeding based on proven benefits unrelated to iron deficiency (see Chapter 56). Pregnant women should receive specific nutritional guidance to enhance fetal and maternal health (see Chapter 56). There is currently insufficient evidence to recommend for or against the routine use of iron supplements for healthy infants or pregnant women who are not anemic ("C" recommendation).

See the relevant background paper: U.S. Preventive Services Task Force. Routine iron supplementation during pregnancy. JAMA 1993;270:2846–2854.

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