comes (eg, growth, cognitive development, and school performance) are currently unavailable and should be a focus of future research. Moreover, there are inadequate data to determine whether giving iron supplements only to pregnant women with documented iron deficiency is less or more cost-effective than routine supplementation. The answer depends on the proportion of women who will require supplements after testing and the costs of the tablets and tests. Modeling studies are also needed to compare the relative effectiveness and cost of routine supplementation and selective supplementation after hematologic and/or iron-storage screening.

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Routine Iron Supplementation During Pregnancy

Review Article

US Preventive Services Task Force

MINERAL and vitamin supplements are prescribed routinely to pregnant women in the United States as a normal part of prenatal care. These supplements are usually prescribed as preparations that include 25 to 65 mg of elemental iron, along with other minerals (eg, calcium, zinc, magnesium, and copper) and vitamins. Few studies have examined the clinical effectiveness of prenatal vitamin preparations as a group. In this report, the US Preventive Services Task Force examines the efficacy and effectiveness of iron in improving outcomes for the mother, fetus, and developing child.

Iron is prescribed routinely, even without laboratory evidence of anemia or iron deficiency, because both conditions are thought to be common during pregnancy; potentially harmful to the mother, fetus, and newborn; and preventable through iron supplementation. The purpose of this review is to evaluate these assumptions, based on current scientific evidence from published clinical research. Recommendations based on this evidence are provided in the accompanying policy statement.[1]

The specific chain of assumptions that underlies routine iron supplementation and form the outline for this review follow:

1. Prevalence: A large number of pregnant women are iron deficient and/or anemic.
2. Burden of suffering: The presence of iron deficiency or anemia in the mother is potentially harmful to the mother, fetus, and newborn.
3. Efficacy: The use of iron supplements can reduce the incidence of these complications, presumably by improving iron stores in the mother, fetus, and newborn.
4. Safety: The potential benefits of iron supplements outweigh their adverse effects.
5. Compliance: Pregnant women will take enough iron during pregnancy to achieve the intended benefits.

This review is intended to provide clinicians with information about the efficacy of iron, either as a component of prenatal vitamin preparations or as a single agent. The value of other constituents in prenatal vitamin preparations (eg, folic acid) is not specifically reviewed, nor does the report address the role of iron-containing foods. The review addresses iron supplementation at any time during pregnancy and is not restricted to a specific trimester. It does not address dietary fac-

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tors that influence iron absorption or behavioral factors that influence compliance with supplementation. The reader is advised that the studies reviewed in this report often use inconsistent or vague definitions of anemia and iron deficiency. Study designs were categorized using the codes of the US Preventive Services Task Force (see Table 2 in accompanying policy statement[1]). Iron dosages in this report refer to elemental iron except where otherwise specified.

PREVALENCE OF ANEMIA AND IRON DEFICIENCY DURING PREGNANCY

Both anemia and iron deficiency are common during pregnancy. Low hemoglobin concentrations are a normal physiologic response to the expansion in plasma volume that occurs during pregnancy. The normal pattern is for hemoglobin concentrations to fall by about 20 g/L, reaching a nadir in the second trimester, and to return to near prepregnancy levels by term.[2] Pregnant women are considered to be anemic when hematologic indexes fall 2 SDs or more below "normal" levels,[2] although definitions for normal vary. In a 1968 report, the World Health Organization[3] defined anemia during pregnancy as a hemoglobin concentration less than 110 g/L. More recently, the Centers for Disease Control and Prevention[4] modified the definition to include hemoglobin concentrations less than 110 g/L during the first and third trimesters and less than 105 g/L during the second trimester, or a hematocrit less than 0.32.

Using either definition, the exact prevalence of anemia among pregnant women in the United States is uncertain, although it is commonly thought to be high. Some have estimated that a hemoglobin level of less than 110 g/L and a hematocrit of less than 0.32 occurs in one third to one half of pregnant women who do not use iron supplements.[5] Data from the Pregnancy Nutrition Surveillance System indicate that a low hemoglobin level and/or low hematocrit is present in 4% of white women and 13% of black women during the first trimester and in 19% of white women and 38% of black women during the third trimester.[6]

The most common cause of anemia among American women is iron deficiency. The average adult woman loses about 14.3 μmol (800 μg) of iron daily as part of normal physiologic losses and an additional 9.0 μmol (500 μg) daily due to menstruation, averaged over the entire menstrual cycle. Pregnant women require an even greater amount of iron due to an expanded red blood cell volume, the needs of the fetus and placenta, and blood loss at delivery.[7] About 1 g of iron is needed to replace net losses during pregnancy, which occur primarily in the second and third trimesters (about 6 mg of iron per day for the 6-month period in women who start pregnancy with absent or minimal storage iron).[2,7] The average nonpregnant woman obtains only about 1.3 mg of absorbed iron per day from the American diet.

The exact prevalence of iron deficiency among pregnant women in the United States is uncertain. Data for nonpregnant women from the National Health and Nutrition Examination Survey[8] suggest that about 5% to 10% of women aged 20 to 44 years are iron deficient. The prevalence in pregnant women is thought to be higher because of the added physiologic demands of pregnancy, but exact data are lacking. Iron deficiency anemia is more common in certain high-risk groups, such as persons of low socioeconomic status or limited education; black or Hispanic persons; women with high parity, or those with a history of menorrhagia or multiple gestations; persons with diets that are low in both meat and ascorbic acid; persons who donate blood more than three times per year; adolescents; and persons who use aspirin regularly.[2]

BURDEN OF SUFFERING

The second premise for routine iron supplementation is that iron deficiency or anemia in the mother can harm the mother, fetus, or developing child. Evidence to support these concerns follows:

Effects of Anemia and Iron Deficiency on the Mother

Among the postulated risks to the mother are increased fatigue and decreased work performance; cardiovascular stress due to inadequate hemoglobin and low blood oxygen saturation; impaired resistance to infection; and poor tolerance to heavy blood loss and surgical interventions at delivery.[5,9-12] There is also a theoretical risk that anemic women are more likely to require blood transfusions (a risk factor for infectious diseases) and emergent cesarean section, but data to support these concerns are lacking.

Iron deficiency anemia may be associated with decreased work productivity. Studies in Africa demonstrated that anemic industrial workers (Hgb <90 g/L) had poorer cardiovascular fitness than nonanemic workers[13] and that iron supplementation reversed these deficits.[14] A study of Indonesian rubber plantation workers[15] demonstrated that anemic workers (Hgb <130 g/L) had significantly poorer endurance on the Harvard Step Test, performed less work, and earned less income than coworkers without anemia. When compared with anemic workers who were treated with placebo, anemic workers who received 100 mg of iron daily for 60 days had significantly lower rates of infectious illness and had improved fitness and work productivity. The relationship of iron deficiency and infection has been discussed in the literature for more than 60 years, but clear evidence of an association is lacking.[16] Studies of iron deficiency have reported lower rates of infection in supplemented children than in controls,[17] but design flaws have raised questions about confounding. Other studies have shown no significant difference in infection rates between supplemented and unsupplemented children.[18]

Few studies of the health effects of iron deficiency have included women. A Swedish survey[19] of 1462 women compared the complaints of 82 anemic women (Hgb <120 g/L) with nonanemic women and found no difference in the incidence of reported infections, fatigue, sleeping difficulties, headache, or work absenteeism. Anemic women were significantly more likely to report low work productivity than nonanemic women (10% vs 5%). Elwood et al[20] found that physical symptoms of anemia are generally unapparent unless hemoglobin values fall below 70 to 80 g/L.

Effects of Anemia and Iron Deficiency on the Fetus and Newborn

The postulated risks of iron deficiency on the fetus relate to the impaired delivery of hemoglobin and thus oxygen to the uterus, placenta, and developing fetus. The effects on the mother and fetus are thought to account for the large body of observational data from epidemiologic studies that link anemia/iron deficiency with low birth weight, prematurity, and other adverse obstetrical outcomes. Beginning with studies of famine victims during World War II, decades of retrospective observational studies have shown that pregnant women with poor nutritional status are more likely to have adverse obstetrical outcomes (eg, preterm birth and perinatal mortality) than well-nourished women.[5] The association between anemia and preterm birth has been well documented for more than 30 years. Most of the studies are cross-sectional observational studies (grade II-2 evidence), in which neonatal health parameters (eg, birth weight, gestational age, and death) are compared with concurrent or antenatal maternal hematologic indexes. Relevant data have been

obtained in developing and industrialized countries.

Developing Countries.—Studies conducted in the developing world have documented outcomes associated with severe anemia during pregnancy. Severe anemia is common in these countries, due largely to malaria and other parasitic diseases. Although simple iron deficiency (the topic of this review) is rarely the primary cause, these data provide useful information about the obstetrical complications of severe anemia. For example, Macgregor[21] measured the hemoglobin level of 3950 pregnant women in Kenya during 1957 through 1961. The incidence of low birth weight (5 pounds 8 ounces [2464 g] or less) was 13% in the normal group (Hgb ≥89 g/L), 32% in the moderate anemia group (Hgb 75 to 88 g/L), and 42% in the severe anemia group (Hgb ≤74 g/L). Neonatal deaths per 1000 live births were 22 in the normal group, 29 in the moderate anemia group, and 50 in the severe anemia group. Stillbirths per 1000 births were 51 in the normal group and 150 and 147 in the moderate and severe anemia groups, respectively. The incidence of preeclampsia was 22% in women with severe anemia, compared with a general incidence of 14%. Low birth weight occurred in about 50% of preeclamptic women with severe anemia, compared with the typical incidence of 19% in preeclamptic women.

More recent cross-sectional studies have found similar results. An Ivory Coast[22] study found that mean birth weight was significantly lower (2881 g vs 3070 g) in newborns of anemic mothers (Hgb <100 g/L) than in nonanemic mothers. An Indian study[23] found that, although mild to moderate maternal anemia (Hgb 61 to 100 g/L) at delivery was not associated with lower birth weight or gestational age, newborns of women with severe anemia (Hgb <60 g/L) had significantly lower birth weight (2183 g vs 2599 g) and gestational age (36.4 weeks vs 37.7 weeks) than newborns of nonanemic mothers (Hgb >100 g/L). A study in malaria-endemic Papua New Guinea[24] found that low birth weight (<2500 g) occurred in 65% of primigravidas with severe anemia (Hgb <80 g/L), compared with 27% in primigravidas with mild or no anemia (Hgb 80 to 140 g/L). A Nigerian study,[25] which compared maternal hematocrit at the first antenatal visit with neonatal mortality in nearly 20 000 births, found that the incidence of neonatal deaths increased from 3% for hematocrits of 0.26 or greater to 20% for hematocrits of 0.14 or lower.

Industrialized Countries.—Studies in the United States and Europe have demonstrated that even mild to moderate anemia can be associated with adverse obstetrical outcomes. Klein[26] reviewed the birth certificates of 68 241 neonates in Georgia during 1945 through 1959 and found birth weights less than 2500 g in 8% of women without anemia (Hgb >100 g/L) and in 14% of anemic women. In 50 000 pregnancies followed by the National Collaborative Perinatal Project of the National Institute of Neurological Disorders and Stroke, the probability of a medical abnormality, fetal death, low birth weight (<2500 g), and preterm birth (≤37 weeks) was higher in women with low and high hemoglobin levels.[27] In Boston, a case-control study[28] involving 8163 women found that anemia (hematocrit ≤0.34) was present in 42% of women with preterm births but only 16% of those with term births. In a case-control study[29] involving 1706 pregnant women in California, the odds ratio for preterm birth was 1.9 (95% confidence interval [CI], 1.2 to 3.0) for anemia at any time during the second trimester. A prospective cohort study[30] involving 826 pregnant women at inner-city clinics in New Jersey reported an adjusted odds ratio of 2.66 (95% CI, 1.2 to 6.2) for preterm delivery and of 3.10 (95% CI, 1.16 to 4.39) for low birth weight among women with iron deficiency anemia.

Studies in Europe have reported similar results. In Wales, a retrospective cohort study[31] involving more than 54 000 pregnancies found that perinatal mortality, low birth weight, and preterm births were more common in women with low hemoglobin levels (<104 g/L) and high hemoglobin levels (>132 g/L) than among women in the normal range (Hgb 104 to 132 g/L). In contrast, a prospective cohort study[32] of 796 women in the Netherlands suggested that low hemoglobin levels were not associated with adverse outcomes. Although low birth weight (<2500 g) and preterm birth (<37 weeks) were more common in women with elevated hemoglobin concentrations (≥8.0 mmol/L), there was no significant difference for normal (Hgb 7.0 to 7.9 mmol/L) and anemic (Hgb ≤6.9 mmol/L) women. Low birth weight occurred in 15% of women with high hemoglobin levels, but it occurred in only 5% and 4% of women with low and normal hemoglobin levels, respectively.

These cross-sectional and longitudinal observational studies provide grade II-2 evidence that anemia during pregnancy is associated with perinatal death, preterm birth, and low birth weight. The consistency of results across different study designs and population samples is noteworthy. There are important limitations, however, to using this type of evidence to postulate that these outcomes are caused by anemia or iron deficiency. Most of the studies do not control for other factors that can cause low birth weight and prematurity (eg, smoking), making it unclear whether anemia and iron deficiency are merely associated with these variables rather than having a direct influence on pregnancy outcomes. Studies in developing countries may also be misleading, since factors associated with malaria and other endemic causes of anemia may be more directly responsible for the observed outcomes than iron deficiency.

Effects of Anemia and Iron Deficiency on the Developing Child

Another postulated risk of anemia and iron deficiency is that mothers with these conditions may give birth to infants with anemia or iron deficiency and that this may result in abnormal child development if the deficiencies are not corrected early.[11] Observational studies[33-38] have shown that iron-deficient infants score poorly during infancy on tests of mental and psychomotor development and that iron supplementation does not correct test scores during infancy. Five-year follow-up studies of children who were iron deficient as infants show that they continue to demonstrate poor mental and psychomotor scores, even if their hematologic status has normalized.[39]

Investigators note that these observational studies do not prove that iron deficiency anemia, and not other factors associated with iron deficiency, causes the poor performance.[39] There is some evidence that iron supplements can improve the cognitive function of children.[40] But even if this is true, it is unclear whether iron supplementation during pregnancy can lower the incidence of iron deficiency in children, since studies have not confirmed a correlation between maternal and neonatal iron stores. Although there is some evidence to suggest otherwise,[41] most studies suggest that pregnant women who are iron deficient are no more likely to give birth to iron-deficient newborns than women who have adequate iron stores.[42-49] Maternal protective mechanisms, in cases other than severe maternal anemia, allow the fetus to achieve proper hemoglobin and iron stores, regardless of maternal values.[2,50] Nor is there evidence of a direct correlation between the intake or storage of maternal iron and the iron content of breast milk.[51-53] There is little direct evidence that pregnant women who take iron supplements give birth to infants or children with improved mental or psychomotor performance. Factors other than the iron status of the mother during

pregnancy appear to account more directly for the iron status of children beyond the neonatal period.

EFFICACY

The third premise for routine iron supplementation is that iron can reduce the incidence of obstetrical complications, presumably by correcting hematologic indexes. Although evidence to date is inconclusive, a large body of data suggest that iron supplements are effective in improving the hematologic indexes of the mother. Longitudinal studies[54-59] in which 30 to 200 mg of iron were given daily have shown a statistically significant increase (10 to 17 g/L) in hemoglobin concentration in women taking supplements. As noted earlier, however, maternal iron supplements do not appear to have a consistent effect on the hematologic status of the fetus or newborn.[2]

The US Preventive Services Task Force sought evidence regarding the ability of iron supplements to improve clinical outcomes in either the mother or newborn (eg, low birth weight and preterm birth). The review did not address the biological effectiveness of iron supplements in changing nonclinical outcomes (eg, hematocrit, hemoglobin, and ferritin levels). The bibliographic sources and the specific inclusion and exclusion criteria that were used in the literature review are available on request. The review sought all observational studies and clinical trials published between 1966 and 1991 in the English-language literature. Studies were excluded if they did not measure clinical outcomes in either the mother or newborn.

The review found limited evidence that iron supplements can reduce the incidence of complications from iron deficiency or anemia. The literature on this topic includes two types of evidence: (1) observational data regarding the incidence of obstetrical outcomes in women who take iron supplements; and (2) clinical trials attempting to prove that iron supplements reduce the incidence of adverse obstetrical outcomes.

Observational Studies of Iron Supplementation and Obstetrical Outcomes

Several observational studies have reported clinical outcomes in pregnant women who used iron supplements. These retrospective and prospective cohort studies (grade II-2 evidence) were conducted in developing and industrialized countries.

Developing Countries.—A previously mentioned Kenyan study[21] found that women with moderate to severe anemia (Hgb ≤88 g/L) had a lower risk of adverse outcomes if they were treated with ferrous sulfate (194 mg). The preterm birth rate was 35% in untreated women and 9% in treated women. Stillbirths per 1000 births were 157 in untreated women and 26 in treated women. The neonatal death rate was unchanged, and there were no significant benefits of treatment for women with mild anemia (Hgb ≥89 g/L). In a retrospective cohort study, Harrison and Ibeziako[60] reviewed the records of 185 Nigerian pregnant women who were hospitalized for severe anemia (hematocrit of 0.6 to 0.25) during the second trimester. Treatment included chloroquine, pyrimethamine, folic acid, and ferrous sulfate. Birth weights below the 25th percentile occurred in 35% of women who responded to therapy (hematocrit greater than 0.30 at delivery) and in 54% of women who remained anemic at delivery (hematocrit of 0.26 to 0.30).

Industrialized Countries.—Taylor and Lind[61] reported two surveys in which the effects of iron supplementation were measured indirectly in women at a British maternity hospital. The first survey involved 200 unselected women: 97 women were already taking iron supplements at the start of the study, and the remainder were asked to not begin supplementation. The investigators found no significant difference in the birth weights of the two groups (3264 g vs 3315 g). The second survey was a retrospective cohort study comparing 50 women who took no supplements with 50 women who used iron and folate. There was no significant difference between the groups in either birth weight (3447 g vs 3459 g) or gestational age (283.9 days vs 285.3 days).

In a prospective, controlled cohort study in Sweden, Kullander and Kallen[62] collected data on 6376 women in Malmo in 1963 through 1965. They found that women who took iron and vitamin supplements were significantly less likely to give birth before 38 weeks than women who did not use such supplements. Preterm births occurred in 6% to 9% of the treatment groups and in 11% to 13% of the control groups. The birth weight of boys (but not girls) was significantly higher in women who took iron and vitamins than in those who took no supplements. A case-control analysis of the data revealed that supplement use was lower among women who had induced abortions and perinatal pathology (stillbirth and major malformations) than among women who gave birth to normal infants. The previously mentioned study by Knottnerus et al[32] found no relationship between the use of iron supplements and either low birth weight or preterm birth.

There are obvious problems with using observational studies to draw conclusions about the clinical effectiveness of iron supplementation. Many lacked statistical power, and interventions differed widely between studies. In some studies, women in the intervention groups received iron along with vitamins, folate, and even antimalarial drugs. Beneficial effects observed in these treatment groups therefore cannot be attributed specifically to iron. More importantly, without proper control for confounding variables, it is difficult to know whether women who took iron supplements had other characteristics (eg, healthier lifestyle) that reduced their risk of adverse outcomes. The necessary study design to control for these variables is a randomized controlled trial.

Clinical Trials

Most clinical trials of iron supplementation have used changes in hematologic indexes as the measure of effect, with only a few examining clinical outcomes. One of the first trials to assess health outcomes used subjective measures. In a double-blind, randomized, controlled trial, Paintin et al[63] studied 173 first-trimester primigravidas who attended a British clinic and who had a hemoglobin level greater than 100 g/L. The women were randomized to receive either 105 mg per day of iron aminoate, 12 mg per day of iron aminoate, or a placebo during weeks 20 to 36. At the 30th week of gestation, a questionnaire asked women about overall well-being, work productivity, dyspnea on exertion, and fatigue. The investigators found no significant difference in the responses of the three groups or in the birth weights of their children.

A randomized controlled trial,[64] which involved about 3600 women at a prenatal clinic in Scotland between 1964 and 1966, randomized the women to five groups that received a placebo, iron only (105 mg/day), and three combinations of folic acid and iron, respectively. Hematologic indexes in the treatment groups appeared to improve. However, in the 2800 patients in whom obstetrical and neonatal complications were reported, the study found no difference between groups in the incidence of adverse outcomes (antepartum and postpartum hemorrhage, abruptio placentae, retained placenta, puerperal fever or sepsis, toxemia, fetal distress, preterm birth, low birth weight, and neonatal death).

In a clinical trial that is only available in English in abstract form, Primbs[65] compared outcomes in 128 pregnant women in three groups that received placebo and two different preparations of iron, respectively, starting at 20 to 24

Causal Chain for Routine Iron Supplementation During Pregnancy

Elements of Causal Chain	Grade of Evidence	Limitations of Evidence
Prevalence: a large number of pregnant women are iron deficient and/or anemic	II-2	Precise data for pregnant women are lacking
Burden of suffering: the presence of iron deficiency or anemia in the mother is potentially harmful to the mother, fetus, and newborn		
Mother	I, II-1	Most studies involve men
Fetus	II-2	Most studies do not adjust for other factors associated with poor pregnancy outcomes
Child	II-2	Studies do not address benefits of maternal supplementation
Efficacy: the use of iron supplements can reduce the incidence of complications, presumably by improving iron stores in the mother, fetus, and newborn	II-2	Most studies do not adjust for other factors associated with poor pregnancy outcomes
	I	Most trials report no benefit but may lack statistical power; trials showing benefit may lack internal or external validity (see text)
Safety: the potential benefits of iron supplements outweigh their adverse effects	II-3	Few data available regarding magnitude of adverse effects
Compliance: pregnant women will take enough iron during pregnancy to achieve the intended benefits	II-3	Data based on self-reports

weeks' gestation. Although hematologic indexes improved in the iron-supplemented women, the study found no significant differences in the length of gestation, duration of labor, type of delivery, fetal head circumference or size, or birth weight.

In a double-blind, randomized, controlled trial in Australia,[66] 146 women attending a prenatal clinic were randomized into five groups that received daily placebo, ferrous sulfate (150 mg), folic acid (0.5 mg), ferrous sulfate and folic acid, or ferrous sulfate and high doses of folic acid (5 mg). Although hematologic indexes improved significantly, no significant differences in fetal outcomes (fetal distress, gestational age, placental weight, or birth weight) were noted among the five treatment groups. The placenta was larger in the anemic women.

Groner et al[67] examined the effects of iron supplements on maternal short-term memory and attention span. Thirty-eight adolescents attending an inner-city pregnancy clinic between 1981 and 1982 were randomly assigned to take either vitamins or a combination of vitamins with 180 mg of ferrous fumarate for 1 month. Before and after treatment, both groups were given six psychometric tests. Both groups showed little improvement in scores with treatment, with the exception of the Digit Symbol and Consonant Trigrams tests, for which the experimental group had more improved scores than controls.

In a quasi-experimental study in India, Agarwal et al[68] assigned 418 pregnant women to a study group that received 60 mg of iron and 500 μg of folic acid daily for 100 days or to a control group that received no supplementation. The women attended six rural health care centers, and three centers were randomly selected to provide the study group and three centers provided the control group. The authors did not describe the randomization method or whether the women in the two groups were comparable by demographic or other variables. They reported that mean birth weight was significantly higher in the study group than in the control group (2.9 kg vs 2.6 kg). A birth weight less than 2.5 kg was reported in 38% of the control group and in 20% of the study group.

In a large randomized controlled trial, Hemminki and Rimpela[69] compared routine and selective prescription of iron during pregnancy. Nearly 3000 women at 27 maternity health centers in Finland were randomized to a "routine" group that was advised to take 100 mg of elemental iron daily beginning by the 17th week of gestation or to a "selective group" that was advised to take iron only if certain hematologic parameters were present. Women in the selective group had lower hematocrit levels, but there were few significant differences in maternal outcomes. Self-estimates of well-being and fatigue, number of sick days, and incidence of fever were similar in both groups. Most other outcomes (duration of labor, oxytocin use, instrumental delivery, fever, and duration of postpartum stay) were also similar in both groups. Women in the selective group were more likely to report poorer overall health and to require transfusion and operative delivery, perhaps because of their lower hematocrit levels.

Gestational age at delivery was greater in the routine group than in the selective group (39.9 weeks vs 39.7 weeks), a difference that was statistically significant, but there was no difference in birth weights. Newborn health status, as measured by Apgar scores, perinatal mortality, incidence of malformations and infections, weight gain, duration of stay in a special care unit, and condition on discharge, did not differ between groups. The authors hypothesized that the higher incidence of complications in the selective group may have been due to nonblinding.

In summary, most clinical trials (grade I and II-1 evidence) of iron supplementation have not demonstrated significant improvements in maternal or neonatal outcomes. Sample sizes in these trials are small, and thus statistical power is generally inadequate to prove that iron supplementation is ineffective. Studies with some evidence of benefit include a trial that showed some improvement on selected psychometric tests, a quasi-experimental study in India that reported improved birth weights with supplementation but that may have been confounded by improper randomization, and the trial by Hemminki and Rimpela. In the latter study, which compared routine and selective iron supplementation, women in the selective group were more likely to report poor overall health, to require transfusion and operative delivery, and to have newborns with reduced gestational age at birth. The difference in gestational age might not have been clinically significant, however, and the authors conjectured that the higher complication rates in the selective group may have been due to nonblinding.

SAFETY

The fourth premise for routine iron supplementation is that the potential benefits outweigh its adverse effects. Iron supplements can cause unpleasant gastrointestinal symptoms (eg, nausea and constipation), but these are dose related and usually occur at higher doses than are recommended for routine supplementation. At a dose of 200 mg of iron per day in three divided doses, symptoms occur in about 25% of individuals, compared with an incidence of 13% among those taking placebos.[7] Iron supplements may complicate preexisting gastrointestinal disorders such as ulcerative colitis. Complications of excessive iron storage, including hemochromatosis and hemosiderosis, are possible but very uncommon in women who take

only oral (and not parenteral) iron supplements.[70,71]

A potential hazard of iron supplements is unintentional overdosage by children in the home. In 1988, poision control centers received 13 416 reports of childhood ingestion of iron or iron-containing vitamins.[72] Most deaths from iron overdosage in the United States occur in children, primarily at 12 to 24 months of age. Although 2 to 10 g is usually ingested in fatal cases, as little as 1 to 2 g can cause death.[7] Iron preparations are often brightly coated tablets and capsules resembling candy that are attractive to young children. Other potential adverse effects of iron have been mentioned in the literature, such as claims that it causes birth defects, cancer, heart disease, infection, metabolic imbalances of other minerals, and harmfully high hemoglobin levels.[27,73-77] Some have expressed the concern that supplements may produce an unjustified feeling of security among some pregnant women that diminishes their attention to healthy diets, or that purchasing supplements might consume money needed for food. Scientific proof of these effects is lacking.

COMPLIANCE

The fifth premise for routine iron supplementation is that pregnant women will take enough iron during pregnancy to achieve the intended benefits. Data regarding compliance with iron supplementation are limited and are primarily self-reported; a recent study[78] found that self-reports of iron use are less than 50% accurate. Hemminki et al[79] administered three consecutive questionnaires throughout pregnancy to Finnish women who were advised to take iron daily. The proportion of women who denied taking any iron in the previous 2 weeks was 70% on the first questionnaire, but 63% to 75% reported taking iron "almost daily" on subsequent questionnaires later in pregnancy. The proportion of women who reported taking iron "every now and then" was 6% to 9%. When women were asked why they had not taken adequate iron, 11% responded "forgot," 8% cited "adverse effects," and 4% answered "did not consider necessary."

In a survey of 344 low-income pregnant women in Massachusetts, Suitor and Gardner[80] found that 16% were already taking supplements before pregnancy. Of the 319 women who had received prescriptions for daily prenatal vitamins, 72% reported taking seven pills per week, 11% reported taking one to six pills per week, and 9% reported taking none. Nearly 5% of the women took 14 to 21 pills per week, apparently misunderstanding the prescription. Of the 135 women who had received prescriptions for daily iron, 20% reported taking seven pills per week, 14% reported taking one to six pills per week, and 9% took none. More than 53% of the women reported taking 14 to 21 pills per week, exceeding the recommended dosage of iron.

CONCLUSION

The quality of the evidence in support of the causal chain outlined at the beginning of this article is summarized in the Table. Recommendations based on these findings and other policy considerations are provided in the accompanying policy statement.[1] The recommendations include priorities for future research, a need that is underscored by the gaps in the evidence identified in this review. Future studies will need to be designed carefully to provide definitive information about the effectiveness or ineffectiveness of iron supplementation during pregnancy.

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