Approaches to Anemia in Pregnancy

JMAJ 52(4): 214–218, 2009

Shiro KOZUMA*1

Abstract

Even in normal pregnancy, the hemoglobin concentration becomes diluted according to the increase in the volume of circulating blood. Since iron and folic acid in amounts necessary for the fetus are preferentially transported to the fetus, the mother is likely to develop iron deficiency anemia and folic acid deficiency anemia. An adult woman has about 2 g of iron in her body. When a woman becomes pregnant, the demand for iron increases, necessitating an additional 1 g. According to the 2005 Dietary Reference Intakes in Japan, the necessary intake of iron in Japanese women is 10.5 mg/day, whereas it is 20 mg during pregnancy. In regard to folic acid, 240 μg is required daily in non-pregnancy and additional 200 μg is needed in pregnancy. No consensus, however, has been reached as to the influences of maternal anemia on pregnancy. In Japan, hemoglobin concentrations of 11.0 g/dl or less and hematocrit of 33.0% or less are considered as anemia in pregnancy, regardless of the timing in the period of pregnancy, and patients should be treated with iron or folic acid therapy. In the West, the prophylactic routine use of iron and folic acid is not uncommon, but its usefulness is not necessarily established. A recent recommendation in Japan is that a daily dose of 0.4 mg of supplementary folic acid be taken during pregnancy for the purpose of preventing impairment of neural tube closures such as spina bifida in fetuses, regardless of whether or not anemia is present.

Key words Iron deficiency anemia, Folic acid deficiency anemia

Introduction

Women go through a variety of physiological changes during pregnancy. Changes in the blood circulatory system are particularly notable, permitting normal fetal growth. Even in normal pregnant women, the hemoglobin concentration decreases with dilution according to the increase in the volume of circulating blood. Since iron and folic acid in amounts necessary to the fetus are preferentially transported to the fetus, the mother is likely to develop iron deficiency anemia and folic acid deficiency anemia. About 20% of pregnant women suffer anemia, and most of the cases are iron deficiency, folic acid deficiency, or both. The administration of iron and folic acid to pregnant women is a controversial issue, and the policy regarding this therapy varies among countries.

This paper provides an overview of iron deficiency anemia and folic acid deficiency anemia. The description of anemia of other types as a complication is left to other papers. Although anemia is not the main symptom of the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, this syndrome is also described briefly because it is clinically important in pregnancy and delivery.

Maternal Changes during Pregnancy

During pregnancy, the circulating plasma volume increases linearly to reach a plateau in the 8th or 9th month of pregnancy. The increment is about 1,000 ml, which corresponds to 45% of the circulating plasma volume in non-pregnancy. The plasma volume decreases rapidly after delivery and is then restored to the non-pregnancy level

*1 Professor, Postgraduate School of Medicine, University of Tokyo, Tokyo, Japan (kozuma-tky@umin.ac.jp).
This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol.137, No.6, 2008, pages 1181–1184).

at about 3 puerperal weeks.

Although erythrocytes and hemoglobin also increase during pregnancy, their increases are slow in the initial half of the pregnancy period, causing relative hydremia, and the hemoglobin concentration and hematocrit are lowest in the 5th to 7th month of pregnancy. In the latter half of the pregnancy period, erythrocytes and hemoglobin increase markedly, and the hemoglobin concentration and hematocrit tend to increase and finally reach normal levels at 6 puerperal weeks. In healthy pregnant women in the US who are taking iron supplements, the 5th percentile values of the hemoglobin concentration and hematocrit are reported to be 11.0 g/dl and 33.0% at 12 weeks of pregnancy, 10.6 g/dl and 32.0% at 16 weeks, 10.5 g/dl and 32.0% at 20 weeks, 10.5 g/dl and 32.0% at 24 weeks, 10.7 g/dl and 32.0% at 28 weeks, 11.0 g/dl and 33.0% at 32 weeks, 11.4 g/dl and 34.0% at 36 weeks, and 11.9 g/dl and 36.0% at 40 weeks.[1] In the US, these values are used as indications of the normal lower limits.

An adult woman has about 2,000 mg iron in the body, 60–70% of which is present in erythrocytes, with the rest stored in the liver, spleen, and bone marrow. When a woman becomes pregnant, the demand for iron increases. Specifically, about 1,000 mg more is required, comprising 300 mg for the fetus and placenta, 500 mg for increased maternal hemoglobin, and 200 mg that compensates for excretion. Therefore, an additional 50% of the amount of iron present in the non-pregnant state should be ingested during pregnancy. This corresponds to an additional intake of 4 mg iron per day. Since the absorption of iron in food is about 10%, the additional oral iron intake necessary for a pregnant woman is calculated to be 40 mg/day. However, according to the 2005 Dietary Reference Intakes in Japan, the necessary intake of iron in Japanese women with menstruation is 10.5 mg/day, whereas it is 20 mg during pregnancy.[2]

Folic acid is plentiful in green and yellow vegetables, fruits, beens, and liver. About 50% of the iron in the body is stored in the liver, and deficiency seldom occurs if a well-balanced diet is maintained. According to the 2005 Dietary Reference Intakes in Japan, 240 μg folic acid is required daily in non-pregnancy and additional 200 μg is needed in pregnancy. It has recently been pointed out that the amount of folic acid in the food consumption of Japanese women is decreasing, and that folic acid deficiency may occur in pregnancy, where folic acid demand is increased.

Influences of Anemia on Pregnancy

Placental weight increases in relation to the severity of maternal anemia. It is presumed that this is because placental growth is promoted to compensate for the lack of oxygen delivered owing to anemia. In contrast, opinion is divided as to the influences of anemia on the maternal body and fetus. No consensus has been reached in spite of years of research on this issue.

In developing countries and in retrospective studies, it has been found that the frequencies of fetal death, low-birth-weight newborns, and premature delivery are significantly higher in cases of maternal anemia.[3] On the other hand, prospective studies in industrialized countries have shown that there is no distinct relationship between anemia and perinatal prognosis. Cases of severe anemia have been included in studies in developing countries or in retrospective studies, whereas most cases of anemia are mild or moderate in prospective studies in industrialized countries. Therefore, it is possible that severe anemia is related to the worsening of perinatal prognosis. However, developing countries have critical problems of poor maternal nutritional status and infectious diseases such as malaria. These conditions are accompanied with anemia, but also include various other factors that can worsen perinatal prognosis, presenting a complex causal relationship. Most cases of anemia in Japan are mild, and it is unclear whether such anemia has any effect on perinatal prognosis.

On the other hand, it has been reported that high hemoglobin concentrations are a more important issue from the viewpoint of perinatal prognosis. Hemoglobin concentrations of 13.2 g/dl or higher at 13–18 weeks of pregnancy are reportedly associated with significantly elevated frequencies of perinatal death, low-birth-weight newborns, premature delivery, and pregnancy-induced hypertension syndrome. It has been pointed out that the absence of decreases in hemoglobin concentration during pregnancy means a lack of sufficient development of hydremia as a manifestation of normal changes associated with pregnancy, and that maladaptation to pregnancy may result in a

worse perinatal prognosis.

Iron Deficiency Anemia

The daily requirement of iron for pregnant women is approximately 20 mg. Given the fact that the reported mean daily intake of iron in Japanese pregnant women is about 11 mg, many women are likely to gradually develop iron deficiency during pregnancy, resulting in iron deficiency anemia. It is said that iron deficiency anemia accounts for 77–95% of all cases of anemia in pregnancy, occurring at a frequency of about 20%.

In Japan, pregnant women usually undergo at least 3 blood tests for maternity health screening. In general, hemoglobin concentrations of 11.0 g/dl or less and hematocrit of 33.0% or less are diagnosed as anemia in pregnancy, regardless of the timing in the period of pregnancy, and patients should be given treatment. In the US, the aforementioned 5th percentile values in normal pregnant women are used as the diagnostic criteria for anemia in pregnancy. When anemia is present, the woman is also examined for serum iron level (normal, 60–200 μg/dl), unsaturated iron binding capacity (UIBC) (normal, 100–270 μg/dl), serum ferritin level (normal values for women are generally 5–80 ng/ml, but 30 ng/ml or higher is considered to be more appropriate in view of iron storage), in addition to erythrocyte count, hemoglobin concentration, and hematocrit. Although hypochromic-microcytic anemia is common, about 20% of patients have normochromic-normocytic anemia.

Since the incidences of special types of anemia are low in Japan, iron therapy is often given to patients with mild anemia without a detailed examination being conducted. Although the administration of oral iron is usually adequate, parenteral administration should be chosen when there is intestinal disease or when oral administration is difficult. In such cases, the necessary dose should be calculated, and overdosing should be carefully avoided. Since concomitant folic acid deficiency is common, this deficiency should be considered, and appropriate treatment given, when patients do not respond to iron therapy. For supplementation of iron storage, serum ferritin levels should be used as indices.

In other countries, the prophylactic routine use of iron is not uncommon, and such routine use has long been discussed. Although hematologic findings, including the hemoglobin concentration, are improved by iron therapy, it remains unclear whether such improvement leads to better perinatal prognosis. No beneficial effects have been observed in randomized controlled trials,[4] similar to the issue as to whether anemia affects perinatal prognosis. Although there is no evidence showing that the prophylactic routine use of iron leads to an improved perinatal prognosis, the general view in the US seems to be that the continuing practice of prophylactic routine iron therapy should not be discontinued, considering bleeding at the time of delivery. However, on the other hand, it also has been pointed out that iron supplements and increased iron storage may lead to higher frequencies of maternal complications (e.g., diabetes).[5]

It has been reported that the use of iron supplements beginning from an early stage of pregnancy prevents the occurrence of immature delivery and low-birth-weight newborns. On the other hand, the "Bible" of obstetrics, *Williams Obstetrics*, states that routine iron use in the latter half of the pregnancy period, when the iron requirement increases, is important, whereas iron should not necessarily be used in the early stage of pregnancy. In Japan, reasonable practices at present may be those of performing a detailed examination for anemic patients found by hematologic tests in an early stage of pregnancy and using iron therapy in patients who have probable iron deficiency, the same as the conventional practices.

Folic Acid Deficiency Anemia

Pernicious anemia is elicited by a deficiency of vitamin B_{12} or folic acid. Since folic acid stores in the body are relatively low, in contrast to the presence of extensive vitamin B_{12} stores, most cases of pernicious anemia in pregnancy occur as a result of folic acid deficiency. The incidence is relatively high, 0.5–26%, and is commonly found in multiparas over 30 years of age. Women with multiple gestation or those on anticonvulsant drug therapy, which inhibits the absorption of folic acid, are susceptible to this disease. Folic acid deficiently anemia is characterized by glossitis, gingivitis, and diarrhea, in addition to the usual anemic symptoms.

Folic acid deficiency anemia is diagnosed on

the basis of increased megaloblasts in peripheral blood and bone marrow as well as hyperchromic-macrocytic anemia in peripheral blood. However, since folic acid deficiency in pregnancy is usually accompanied by iron deficiency, it is rather unusual to observe megaloblasts in peripheral blood. A definitive diagnosis can be obtained by bone marrow aspiration if necessary.

Folic acid deficiency anemia is treated by the administration of folic acid at a dose of 500–1,000 μg/day. Reticulocytes appear within 4 days of therapy, and the maximum response is reached within one week of therapy. About two-thirds of patients with folic acid deficiency anemia have concomitant iron deficiency anemia, and receive simultaneous iron therapy.

The Ministry of Health, Labor and Welfare (MHLW) in Japan has issued a notice that recommends the administration of folic acid in pregnant women, regardless of whether or not anemia is present.[6] In other countries, mainly in Europe and North America, etiological studies have shown that folic acid intake lowers the risk of impairment of neural tube closures such as spina bifida in fetuses, and it is recommended to increase folic acid intake in women of childbearing age.

In Japan, the incidence of spina bifida is relatively low. Since the prophylactic benefit of folic acid administration is said to be low in regions where its incidence is low, folic acid intake has not been promoted in this country. However, a study carried out in southern China, where the incidence of spina bifida is as low as that in Japan, demonstrated that the risk of developing this condition was reduced by folic acid intake. In addition, there has recently been a trend toward an increase in the incidence of spina bifida in Japan, and diversified eating habits have resulted in a concern that increasing numbers of individuals do not have adequate folic acid intake. Considering these aspects, the MHLW has stated that the ingestion of folic acid supplements at a daily dose of 0.4 mg in addition to folic acid intake from food is expected to lower the risk of developing this condition. However, since generation of the fetal central nervous system occurs by the 7th weeks of gestation, the important period of folic acid intake is at least 1 month before pregnancy until 3 months after the beginning of pregnancy.

Currently, folic acid administration is not a widely accepted practice in Japan, but seems likely to become more common in the future, based on the above recommendation of the MHLW.

Anemia of Other Types

Anaplastic anemia and hemolytic anemia can also occur during pregnancy. In particular, the possibility of hemolytic anemia due to thalassemia, sickle cell anemia, and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should also be borne in mind if the patient is not Japanese.

HELLP is a syndrome characterized by hemolysis, elevated liver enzymes, and low platelet count that can occur from the late pregnancy period to the puerperal period. Pregnancy-induced hypertension syndrome is often, but not always, concomitant, and the mechanisms of such occurrence remain unclear. When left untreated, disseminated intravascular coagulation (DIC) progresses, and carries a poor prognosis (maternal mortality, 1.8–24.2%; perinatal mortality, 7.7–60%). Right hypochondrial pain, epigastric pain, nausea, and vomiting may be the initial symptoms.

Sibai advocates that diagnostic criteria include bilirubin 1.2 mg/dl or higher and LDH 600 U/l or higher as hemolytic findings, presence of acanthocytes in peripheral blood smears, the liver enzyme GOT 70 U/l or higher, and platelet count of 100,000/μl or lower.[7] In treatment, early termination of pregnancy is very important. In addition, other treatments to relieve the respective symptoms should be given. Treatment of DIC is often necessary.

Conclusion

Iron supplements are not routinely given to pregnant women in Japan. When blood tests in an early stage of pregnancy reveal anemia, detailed examination is carried out if necessary, and iron therapy is given. Based on the fact that the prophylactic effect on impairment of neural tube closure in the fetus has been advocated, simultaneous administration of folic acid should also be considered. Anaplastic anemia and hemolytic anemia should be excluded because concomitant anemia of these types occurs accidentally, although in rare cases. Antenatal care of pregnant women is obviously important, and importance of health care in women prior to pregnancy has been gradually recognized from various health related areas.

References

1. Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 1989;38:400–404.
2. 2005 Dietary Reference Intakes in Japan. Tokyo: Dai-Ichi Shuppan Publishing. Co. Ltd.; 2005. (in Japanese)
3. US Preventive Services Task Force. Routine iron supplementation during pregnancy. Review article. JAMA. 1993;270:2848–2854.
4. Mahomed K. WITHDRAWN: Iron supplementation in pregnancy. Cochrane Database Syst Rev. 2007;18(3):CD000117.
5. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am J Clin Nutr. 2005;81:1218S–1222S.
6. Notice from the Children and Families Bureau, Ministry of Health and Welfare "Promotion of the provision of appropriate information about folic acid intake in women of childbearing age to reduce the risk of developing impairment of neural tube closure" (No. 72, No. 78), Dec 28, 2000. (in Japanese)
7. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol. 1990;162:311–316.