Do healthy pregnant women need iron supplementation?

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Iron, indispensable for energy production, oxygen transportation, and DNA synthesis, and other trace elements, such as folic acid, vitamin, iodine, calcium, and zinc, are significantly increasingly demanded in pregnant women.[1,2] Iron deficiency anemia (IDA) is associated to >16 million pregnant women worldwide per year.[3] Strategies to address concurrent trace element deficiencies and/or IDA in pregnancy, including food fortification and prenatal supplementation with iron and/or other trace elements, have been explored. However, it remains uncertain whether iron supplementation of pregnant women can improve maternal and prenatal outcome or not, especially for those women who do not have anemia or trace element deficient status. Therefore, any study focusing on the iron supplementation for pregnant women is welcome. We are happy to introduce the study by Asadi et al,[4] published in the last November issue of the *Journal of the Chinese Medical Association*, on the investigation of outcome of nonanemic pregnant women after prophylactic iron supplementation. The authors performed a prospective nonrandomized study to compare the maternal and neonatal outcome between relatively healthy pregnant women with/without active iron supplementation during the pregnancy, and in addition, maternal and neonatal outcome of IDA pregnant women treated with standard iron supplementation was also evaluated. The authors found that normal healthy women undergoing active iron supplementation failed to obtain additional benefits in regard of maternal and neonatal outcome but might be increasing risk of gestational diabetes mellitus (GDM). This study is interesting and worthy of discussion.

First, anemia is common and affects up to 50% of pregnancies.[3,5] However, there is ongoing debate on the optimal approach to identify anemia in pregnant women. The common definition of anemia in pregnancy comprises a laboratory threshold of hemoglobin (Hb) below which treatment is offered or based on laboratory values taken from a healthy population where two standard deviations below the lower limit of normal distribution.[5] There are limited data on the use of other laboratory tests, such as serum ferritin, transferring levels or others for defining anemia, because there is considerable variation in serum ferritin thresholds recommended by different expert groups to diagnose IDA.[6] The most commonly used thresholds of serum ferritin was <12 (35 studies) or <15 ng/mL (17 studies), respectively. However, the other cutoffs are also found, such as <20 (8 studies) and <30 ng/mL (6 studies), although they are less commonly used.[5] We are wondering why the ferritin cutoff value was <30 ng/mL used by authors,[4] because studies showed the recommended serum ferritin cutoff of <15 ng/mL might be more specific, but not sensitive,[7] although recent UK guidelines on the management of iron deficiency recommended that a serum ferritin level of <30 ng/mL in pregnancy is indicative of iron deficiency.[8] In addition, we found all women in three groups have Hb serum levels >12 gm/dL (mean 14.75, 12.24, and 12.54 gm/dL in every group).[4] It is hard to convince us that women in any group had anemia, based on UK guidelines on the management of iron deficiency (Hg < 11 gm/dL in first trimester and <10.5 gm/dL in second and third trimesters) in pregnancy.[8] The value of measurement of serum ferritin should be performed in women with a known hemoglobinopathy to identify concomitant iron deficiency and exclude iron loading states, since high iron states may mediate these events, including oxidative stress, increased blood viscosity, and suboptimally effective systemic response to inflammation and infection.[9–13] It is not surprising to read the increasing risk of GDM in nonanemia pregnant women who have been treated with iron supplementation in routine in the current article.[4] One meta-analysis showed women who had GDM compared to pregnant women did not have an increased standardized mean differences (SMD) of iron with 0.25 μg/dL (95% confidence interval [CI] 0.001-0.50), an increased SMD of ferritin with 1.54 ng/mL (95% CI 0.56-2.53), an increased SMD of transferrin saturation with 1.05% (95% CI 0.02-2.08), and an increased SMD of Hb with 0.81 g/dL (95% CI 0.40-1.22).[14] After adjustment, adjusted odds ratio for GDM were 1.58 (95% CI 1.20-2.08) for ferritin, 1.30 (1.01-1.67) for Hb, and 1.48 (95% CI 1.29-1.69) for dietary heme intake, supporting that

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iron loading might be positively correlated with the risk of GDM in pregnant women.

Second, although healthcare professionals should be aware that IDA in pregnancy is common and associated with increased risk of maternal and perinatal morbidity and mortality, and might has important implications for the future neurodevelopment of the infant,[8] the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition concluded that there is no evidence that iron supplementation of pregnant women improved iron status in their offspring in a European setting,[15] suggesting iron supplementation in pregnant women should be weighed by benefits and risks ratio in different race, countries, and socioeconomic status.

Taken together, trace elements and heavy metals are essential for pregnant women.[16] Any recommendation for supplementation of any one of these micronutrients should be based on the clinical evidence. Randomized trials investigating the benefits of iron supplementation or iron reduction in certain-population pregnant women at IDA or at high risk for GDM are warranted.

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