The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy

Shuxiang Li, Xin Gao, Yancai Wei, Gengchao Zhu and Chen Yang*

Department of Nuclear Medicine, Suzhou Hospital Affiliated to Nanjing Medical University, 215002 Suzhou, China
(Received March 13, 2016)

Summary Previous studies have identified an association between iron deficiency and thyroid function. We aimed to determine if there is a relationship between iron deficiency and thyroid function during the first trimester of pregnancy. Two thousand five hundred eighty-one pregnant women who presented for the first prenatal care were enrolled and divided into three groups, the mild iron deficiency (MID) group, iron deficiency anemia (IDA) group and normal control (NC) group, according to serum ferritin and hemoglobin levels. The former two groups can be merged into one iron deficiency (ID) group. Thyroid function parameters were compared among the three groups, including free thyroxine (FT4), thyroid stimulating hormone (TSH), total thyroxine (TT4) and thyroid peroxidase antibodies (TPOAb). Moreover, the rates of thyroid dysfunction were also compared. Our results show that pregnant women in the MID and IDA groups have higher TSH and lower FT4 status than those in the NC group \((p<0.01)\), and the difference between the IDA group and MID group is significant \((p<0.05)\). TPOAb in the IDA group is higher than in the MID group and NC group. Meanwhile, the rate of hypothyroidism or subclinical hypothyroidism in the IDA group was significantly higher than in the MID group and NC group \((p<0.01)\). And the positive rate of TPOAb is also higher in the IDA group than MID group and NC group \((p<0.05)\). Iron deficiency is related to thyroid function and could lead to hypothyroidism during early pregnancy, which could be explained by thyroid autoimmunity.

Key Words iron deficiency, thyroid, early pregnancy

Iron deficiency remains a major public-health problem worldwide, particularly in developing countries (1). An increasing number of studies is pointing to an association between iron deficiency and thyroid function. Previous rodent experiments and human studies (2–6) have shown that iron deficiency impairs thyroid metabolism. In some iodine-sufficient areas, endemic goiter is still prevalent where low serum ferritin concentrations exist (7, 8).

On the other hand, pregnant women have greater nutrient demands and are at great risk for iron deficiency. In a study of Swiss pregnant women in the second and third trimester, Zimmermann et al. (9) reported that poor maternal iron status predicts both higher TSH (thyroid stimulating hormone) and lower TT4 (total thyroxine) concentrations. Yu et al. (10) reported that serum FT4 (free thyroxine) levels were significantly lower in pregnant women with ID (iron deficiency) compared with the corresponding groups without ID. However, the number of related studies remains very small, especially for subjects in the first trimester. To address this, the study was undertaken to investigate the relationship between iron deficiency and thyroid function during the first trimester.

MATERIALS AND METHODS

Subjects. The study was carried out in the city of Suzhou in China, an area which is iodine-sufficient. Between December 2014 and February 2015, all pregnant women coming for prenatal care in Suzhou Hospital Affiliated to Nanjing Medical University were invited to enroll in this study. They were asked to donate an additional fasting blood sample for further study during the routine blood collection at the first antenatal visit \((\leq 12\text{th wk gestation})\). Women with a history of thyroid disorders or on medications that might alter thyroid functions or iron metabolism were excluded from the study. Among these participants, 2,654 were enrolled. This study was approved by the Institutional Review Board of Suzhou Hospital Affiliated to Nanjing Medical University.

Methods. Blood samples were obtained in the morning. Serum concentrations of ferritin (Beckman-Coulter, Inc, Brea, CA) and FT4, TSH, TT4, TPOAb (thyroid peroxidase antibodies; Abbott Diagnostics, Sydney, NSW) were measured by means of chemiluminescent immunoassay. The fundamental data for anemia including hemoglobin (Hb), red blood cell count (RBC), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were detected by biochemical assay (Sysmex, Kobe, Japan).
There are currently no agreed criteria for iron deficiency and in this study a serum ferritin concentration of <20 μg/L was considered to indicate deficiency. In addition, the diagnosis of IDA (iron deficiency anemia) also requires an Hb concentration of <110 g/L. Those women with ferritin >20 μg/L and Hb <110 g/L were excluded. Of the 2,654 participants of this study, 73 were excluded, leaving a final total of 2,581 subjects.

Guidelines of the American Thyroid Association (ATA) recommended 0.1–2.5 mIU/L as the specific reference ranges in the first trimester for TSH (11). The trimester-specific reference ranges are 11.49–18.84 pmol/L for FT4, and 62.68–230.00 nmol/L for TT4. And the threshold value of TPOAb is 5.61 IU/mL.

Thyroid dysfunction includes 1) overt hypothyroidism (elevated TSH levels combined with decreased FT4 levels or serum TSH $\geq 10$ mIU/L), 2) subclinical hypothyroidism (elevated TSH levels combined with normal FT4 levels), though overt hypothyroidism and subclinical hypothyroidism can be unified to hypothyroidism, 3) overt hyperthyroidism (decreased TSH levels combined with elevated FT4 levels), 4) subclinical hyperthyroidism (decreased TSH levels combined with normal FT4 levels), though overt hyperthyroidism and subclinical hyperthyroidism can be unified to hyperthyroidism and 5) TPOAb positivity.

Stages of iron deficiency can be characterized as mild deficiency where iron stores become depleted but hemoglobin levels are normal and iron deficiency anemia where synthesis of hemoglobin is decreased and oxygen transport to the tissues is reduced (12).

**Results**

In this study, 2,581 participants were included, with the age range being 18–44 y. Sixteen point seven percent of them had ferritin levels <20 μg/L, among whom were 376 with mild iron deficiency (MID group) and 55 with more advanced iron deficiency anemia (IDA group). Table 1 gives the baseline characteristics of the study subjects and the comparison of anemia examinations among different groups according to iron status. The age and BMI were similar among the three groups. There was significant difference in the comparison of anemia examinations.

The thyroid function indexes are compared in Table 2. Serum TSH concentrations were higher and FT4 were lower in subjects with iron deficiency (both the MID and
Iron Deficiency and Thyroid Function during Early Pregnancy

IDA groups) than for the normal control (NC) group (p<0.01), and there was significant difference between the IDA and MID group (p<0.05). TPOAb was higher in the IDA group than in the MID and NC group (p<0.05), while TT4 was not significantly different among groups.

Table 3 compares the prevalence of thyroid dysfunction among the three groups. The rate of hypothyroidism or subclinical hypothyroidism was higher in the IDA group than in the MID and NC group (p<0.01), while TT4 was not significantly different among groups.

Table 3 compares the prevalence of thyroid dysfunction among the three groups. The rate of hypothyroidism or subclinical hypothyroidism was higher in the IDA group than in the MID and NC group (p<0.01), while TT4 was not significantly different among groups. The conclusion that the rate of hypothyroidism or subclinical hypothyroidism and positive TPOAb were not significantly different between the MID and NC group might indicate that the stage of iron deficiency also has an influence on the above mechanism and that iron deficiency anemia has more obvious effects on thyroid autoimmunity and thyroid function than does mild deficiency.

DISCUSSION

Worldwide, iron deficiency is still recognized as a public health concern with a high prevalence, affecting nearly 2 billion people (13). Among them, pregnant women are the most vulnerable because of the increased needs of the fetus.

Iron is an essential microelement for life and iron deficiency is related to alterations in many metabolic processes and results in impairment of cognitive performance and behavior, immune function, thermoregulation and exercise or work capacity (14). In addition, iron-deficiency anemia is the most severe consequence of iron deficiency and the most common kind of anemia. The prevalence of iron-deficiency anemia in different regions of the world ranges from 12 to 43% (15). Numerous and compelling scientific evidence has shown that IDA during pregnancy is linked with a wide variety of adverse maternal and perinatal outcomes, such as preterm birth, low birth weight and unhealthy neurodevelopment in the fetus (16). And it is now clear that neonatal iron stores can be compromised when the mother is iron deficient or anemic (17).

At the same time, growing research suggests that iron deficiency with or without anemia impairs thyroid metabolism. IDA affects thyroid hormone status by decreasing plasma T3 and T4, reducing peripheral conversion of T4 to T3 and increasing TSH concentrations (5). Iron deficiency is a possible contributor to endemic goiter. However, the specific mechanism is unclear. ID may affect thyroid metabolism by inducing alterations in the common hypothalamic–pituitary–thyroid (HPT)
axis (2), reducing T3 binding to hepatic nuclear receptors (18) or through anemia and lowered oxygen transport, similar to thyroid impairment in hypoxia (19). ID may also impair the activity of hepatic T4-5′ deiodinase, an enzyme responsible for the conversion of T4 to T3 (20), or the activity of thyroid peroxidase, which is iron-dependent and responsible for thyroid hormone synthesis (4).

Meanwhile, iron supplementation improves thyroid function. A series of intervention studies has shown that iron supplementation improves the efficacy of iodized oil and salt on children with goiter (21, 22). Iron treatment in women with subclinical hypothyroidism was proven to provoke a minor increase of T4 and a mild decline of TSH (23). A recent controlled trial study in iron-deficient adolescent girls indicated that improvement of iron status was accompanied by an improvement in some indices of thyroid hormones, including T4, T3 and rT3 (24).

On the other hand, hypothyroidism itself can cause a wide variety of anemic disorders, and numerous mechanisms are involved in the pathogenesis (25). Iron deficiency anemia can result from impaired intestinal iron absorption related to thyroid hormone deficiency or associated gastric achlorhydria. Therefore, the thyroxine supplementation turns out to be important, while the related research remains very limited. This mechanism should be included in further study.

In the present study, serum FT4 concentrations were lower and TSH concentrations were higher in subjects with iron deficiency, in line with previous studies (10, 20, 26) and the difference between the IDA group and MID was significant. TT4 levels were not significantly different among different groups, which may be relevant to the specific status during early pregnancy. T4 binding globulin (TBG) concentrations increase by weeks 6–8 and remain high until delivery (11), leading to the increase of TT4 and making TT4 no longer suitable for the exact assessment of the levels of circulating thyroxine. In contrast, FT4 is independent of variations in TBG and may better reflect the circulating thyroxine levels. One important finding in this study is the significantly higher incidence of subclinical hypothyroid dysfunction for iron deficiency. The results suggest that hypothyroidism is a common finding during early pregnancy and confirm that iron deficiency, especially when the stage reaches iron deficiency anemia, is associated with thyroid function during pregnancy. The results also reveal a similar conclusion with the positive rate of TPOAb, indicating the possible effect of iron deficiency on thyroid autoimmunity and making it possible that the high rate of hypothyroidism can be explained by thyroid autoimmunity.

The present study has several limitations. Its cross-sectional nature and small sample size limit the findings. Meanwhile, some parameters such as transferrin receptor and total iron binding capacity were not measured; the assessment of iron status would be more accurate with the measurement of them. The thyroglobulin antibody could better verify the effect of iron deficiency on thyroid autoimmunity. Further study should include data reflecting nutritional condition, such as albumin, and a further focus may be on the effects of thyroxine supplementation.

In conclusion, the present study is the first report to show that iron deficiency can result in hypothyroidism during early pregnancy. Therefore, routine thyroid monitoring and appropriate iron supplementation should be recommended for iron-deficient pregnant women to avoid more adverse pregnancy outcomes.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES
Iron Deficiency and Thyroid Function during Early Pregnancy

244: 82–89; discussion 89.


