

Research Progress on the Clinical Treatment of Iron Deficiency Anemia in Pregnancy by Combining Chinese and Western Medicine

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Abstract: Iron deficiency anemia (IDA) is a relatively common nutritional disorder during pregnancy, which can cause immediate and long-term adverse effects on the mother, fetus, and neonate. It is a key factor leading to adverse maternal pregnancy outcomes and adverse fetal and neonatal outcomes. Therefore, active, effective, and standardized treatment of IDA is crucial for pregnant women. In this article, we summarize the latest clinical research progress on the treatment of iron-deficiency anemia during pregnancy using traditional Chinese medicine, Western medicine, and the combination of Chinese and Western medicine over the years, with the aim of providing a reference for clinical diagnosis, treatment, and prevention.

Keywords: Pregnant women, iron deficiency anemia; Blood deficiency; Chlorosis; Combination of Chinese and Western medicine; Clinical treatment; Research progress.

1. Introduction

Iron deficiency anemia (IDA) is particularly prevalent as a clinical condition, accounting for almost 95% of the proportion of anemia cases in pregnancy and is one of the most common nutritional disorders worldwide [1]. The increase in maternal blood volume and the substantial elevation of iron demand are important causes of IDA in pregnancy [2]. It can be categorized into three stages based on the level of iron stores in the pregnant woman: the first stage is iron reduction; the second stage is iron deficiency erythropoiesis and the final IDA state [3]. Failure to receive timely and effective intervention can significantly increase the likelihood of risks such as hypertension-related disorders in pregnancy, early amniotic membrane rupture, puerperal infections, and postpartum mood disorders [4]; in addition, it can also pose a series of serious challenges to the fetus and neonate, including, but not limited to, fetal growth retardation, intrauterine hypoxia, the risk of stillbirth, preterm labor issues, and the potential for neonates to experience hypoxic brain damage and other health threats [5-7]. Therefore, it is important to pay great attention to this global public health problem. In traditional Chinese medicine, there is no clear record of iron deficiency anemia in pregnancy, but modern Chinese medicine attributes it to "blood deficiency", "consumptive disease", "Chlorosis" and "palpitation" according to its symptomatic characteristics. The pathogenesis is mainly for congenital endowment deficiency, deficiency of essence and blood; acquired weakness of the spleen and stomach, insufficient qi and blood source; prolonged illness and fatigue, essence and blood dark depletion [8]. A number of studies have confirmed that Chinese medicine therapy has similar effects to iron for IDA in pregnancy with fewer side effects, and also promotes iron absorption, and this paper will discuss the treatment of IDA from the perspective of combining Chinese and Western medicine.

2. Treatment of Iron Deficiency Anemia in Pregnancy by Western Medicine

At present, there is no uniform standard for the diagnosis of IDA in pregnancy, according to China's guideline recommendation, the hemoglobin (Hb) concentration of pregnant women <110g/L is defined as anemia, and according to the Hb concentration, the anemia in pregnancy can be divided into: mild anemia (100-109g/L), moderate anemia (70-99 g/L), severe anemia (40-69g/L), and severe anemia (<40g/L), and IDA is diagnosed as anemia in pregnancy when the diagnostic standard of anemia is met and serum ferritin <20ug/L. Therefore, the treatment of IDA in pregnancy should be in accordance with the current status of iron deficiency anemia in western medicine. The diagnosis of IDA in pregnancy was made when serum ferritin was <20ug/L while meeting the diagnostic criteria for anemia; therefore, in treating IDA in pregnancy, the appropriate treatment plan should be selected according to the grade of anemia, and the primary treatment strategy for patients with mild-to-moderate IDA is to use oral iron supplements, supplemented by iron-rich diets; while for patients with severe IDA, it is recommended that oral iron supplements or intravenous iron therapy be considered, and the secondary treatment strategy for patients with severe IDA is oral iron supplements or intravenous iron therapy. For patients with severe IDA, it is recommended to use oral iron or consider intravenous iron therapy, followed by small-dose multiple transfusions of concentrated red blood cells. As for those with extreme severe anemia, the first step is to carry out red blood cell concentrate transfusion immediately, wait for the hemoglobin (Hb) level to rise to 70 g/L, and after the clinical symptoms show obvious improvement, then convert the red blood cell concentrate transfusion as appropriate. After the hemoglobin (Hb) level has risen to 70 g/L and clinical symptoms have shown significant improvement, the patient should then be converted to oral iron or continued intravenous administration, as appropriate. In clinical practice, until the hemoglobin level has completely normalized, it is recommended that oral iron

be continued for 3 to 6 months during the recovery period or until approximately 3 months postpartum to consolidate the efficacy of the therapy and prevent recurrence [9, 10]. When other causes of iron deficiency have been ruled out one by one and iron therapy is ineffective, Iron Refractory Iron Deficiency Anemia (IRIDA) due to a variant in the Tmprss6 gene should be considered, and gene sequencing can be performed to genetically analyze the cause of the disease [11, 12].

2.1 Oral Iron Therapy

Oral iron therapy has the advantages of being convenient, inexpensive, and safe, making it the treatment of choice for IDA in pregnancy. Commonly used iron agents include two main categories: organic iron: ferrous sulfate; and inorganic iron preparations, covering: polysaccharide iron complex, protein iron succinate, ferrous succinate, ferrous fumarate, ferrous gluconate, ferrous lactate, ferrous dextrose anhydride and other forms of iron, ferrous iron salts with high bioavailability, is often the first choice of preparations [13, 14]. The recommended daily supplemental dose for IDA patients in singleton pregnancies is 100 to 200 mg, and the dose may be increased in multiparous pregnancies, but need not be doubled. However, oral iron may cause gastrointestinal discomfort such as nausea, vomiting, heartburn, constipation, black stools, and increased risk of enterocolitis, leading to poor compliance, and therefore the efficacy of treatment should be assessed with regular blood tests after 2-4 weeks of treatment [15, 16]. In general, if the hemoglobin concentration does not increase by 10 g/L within 2 weeks or by less than 20 g/L within 4 weeks, it is necessary to consider the possibility of absorption dysfunction, poor compliance, blood loss, lack of hematopoietic material, and other types of anemia, which should be investigated and clarified in a timely manner. Ferritin is a key regulator of iron homeostasis. High serum hepcidin levels affect iron utilization and reduce iron absorption, and hepcidin levels are lowest during fasting in the early morning, when oral iron can be administered once daily or every other day for best results [17]. At the same time, the intake of vitamin C and vitamin D can be increased, which can help to promote the absorption and utilization of iron, thus enhancing the clinical therapeutic effect [18, 19].

2.2 Iron Injection Therapy

Intravenous iron should be considered in pregnant women who are intolerant to oral iron, have poor compliance, ineffective treatment, and have IDA diagnosed after 34 weeks of gestation with Hb <100 g/L [20]. Although the commonly used second-generation intravenous iron agents, such as low molecular iron dextran and iron sucrose, can effectively improve IDA, there are adverse reactions such as headache, dizziness, venous thrombosis, local reactions at the injection site, and occasional fatal allergic reactions leading to cardiac arrest and death, and the need for low-dose, multiple intravenous infusions increases the cost of treatment and the number of visits to the doctor, which often leads to its limited clinical application [21]. Three generations of novel intravenous iron agents, ferric carboxymaltose and ferric isomaltose anhydride, and other iron-carbohydrate composite drugs, can maximally inhibit the release of non-transferrin-bound iron and free iron, and effectively

reduce the incidence of infusion adverse reactions due to free iron, even in the context of high-dose administration [22, 23]. Clinical trials have demonstrated that novel intravenous iron supplements can rapidly restore maternal iron stores, improve hemoglobin concentration, ferritin levels, transferrin saturation, and improve maternal fatigue, and are safer, with better therapeutic efficacy, lower incidence of adverse events, better adherence, and lower economic costs than iron sucrose, although the risks of hypersensitivity reactions and hypophosphatemia need to be guarded against [24]. The use of this type of iron should be based on the instructions of the drug and should not exceed the recommended dosage, and should be avoided in individuals with a history of allergy to injectable iron, in the early stages of pregnancy, with acute or chronic infections, or with chronic liver disease. Studies have shown that intravenous iron increases Hb concentration more and more rapidly than oral iron, and is better able to avoid adverse maternal outcomes and adverse effects [25, 26]. However, there is no conclusive evidence of its effectiveness on individual maternal outcomes or neonatal outcomes, and more research is needed to elucidate the impact on clinical outcomes [27].

2.3 Blood Transfusion Therapy

There is no global consensus on the standardization of hemotherapy. According to the clinical practice guidelines in China, blood transfusion therapy is recommended when a patient's hemoglobin concentration is below 70 g/L [28]; and for patients whose hemoglobin level is within the range of 70-100 g/L, the decision of whether or not to implement blood transfusion should be based on a comprehensive judgment of whether or not they are about to undergo an operation, the condition of their heart function, and other specific factors [29]. In contrast, foreign medical consensus and guidelines indicate that severe anemia in which the mother's hemoglobin level falls below 60 g/L is closely related to insufficient oxygen supply to the fetus, which may lead to serious consequences such as fetal heart rate abnormalities, amniotic fluid reduction, fetal cerebral vasodilatation, and even fetal death, and therefore blood transfusion is strongly recommended at this level [30, 31].

3. Current Status of TCM Treatment of Iron Deficiency Anemia in Pregnancy

Traditional Chinese Medicine (TCM) considers chlorosis to be a deficiency disease, locating it in the spleen and stomach, and relating it to the liver and kidneys, following the treatment principle of "treating deficiency with tonification." "Plain Questions" state: "Qi commands the blood, and blood is the mother of Qi." This illustrates that Qi and blood are interdependent and closely related; Qi not only generates blood but also aids in hemostasis. Therefore, those with blood deficiency should first replenish their Qi. Women are blood-based, the liver stores blood, the spleen produces blood, and the kidney stores refined blood. The spleen provides the material basis for the acquired constitution, which is responsible for the transportation of water and grain. It forms the basis for the generation and transformation of Qi and blood. The spleen's function in transporting water and grain is directly related to the production of nutritive Qi and fluid and humor, both of which are essential components of blood

formation. Negligence in the healthy functioning of the spleen and stomach can lead to a lack of blood and biochemical sources. Kidney essence is also the basic substance that transforms blood. The kidneys store essence, from which marrow is produced, and the marrow then transforms the blood. Since the liver and kidneys share the same origin, essence and blood nourish each other. In addition, intestinal parasites such as hookworms invading the human body can also lead to impaired functions of the spleen and stomach, failure in transportation and transformation, which further aggravates blood deficiency. Coupled with the depletion of yin and blood after pregnancy to nourish the fetus, the blood supply for the fetus further weakens the mother's vital essence and blood, making her more susceptible to this disease. Therefore, for the treatment of blood deficiency in pregnancy, traditional Chinese medicine (TCM) practitioners tend to use the methods of replenishing qi and nourishing blood, strengthening the spleen and harmonizing the stomach, tonifying the spleen and benefiting the kidneys, and nourishing the liver and kidneys [32-34].

3.1 Invigorating Qi and Nourishing the Blood

Jiang [35] believed that the treatment of IDA focused on supplementing qi and blood, and the Eight Pieces Decoction was used to add or reduce according to the clinical syndrome. The formula included angelica sinensis, ginseng, poria, white atractylodes, Licorice, Shudi, Paeoniae, Chuanxiong, etc. It can regulate Rongwei, nourish qi and blood, supplement deficiency and damage, and has a remarkable clinical effect on IDA. Du et al. [36] clinically selected 62 patients with IDA with deficiency of Qi and blood, and administered Angelica Buxue Decoction and Guipi Decoction orally, once a day, morning and evening after meals, for continuous treatment for 2 months. The results showed that the Chinese medicine group significantly reduced adverse reactions and significantly improved clinical TCM symptoms.

3.2 The Method for Strengthening the Spleen and Stomach

Tang et al. [37] treated IDA by targeting the spleen and stomach, and believed that the weakening of the spleen and stomach was the primary pathogenesis of the disease. They considered the spleen and stomach to be the origin of Qi and blood production. Strengthening the spleen not only regulated gastrointestinal function but also promoted the absorption and utilization of hematopoietic raw materials. The Four Gentlemen Decoction was recommended to regulate the spleen and stomach, with specific prescriptions including ginseng, white atractylodes, poria, and licorice, among others. Tang's etc. [38] in the treatment of IDA emphasize the spleen and stomach, commonly using Guipi decoction and Danggui Buxue decoction to treat the disease. It is believed that spleen deficiency can be divided into two types: primary spleen deficiency and acquired spleen injury. In the treatment of acquired spleen injury, pathological products should be removed based on strengthening the spleen. If dampness and phlegm are also present, clear dampness and heat with Gentian purging liver soup; for food accumulation, use Baohu Pill.

3.3 Nourishing the Spleen and Kidney Method

Prof. Sun [39] used the method of "tonifying the spleen and kidney, acidifying blood" to treat IDA in clinical syndromes, with the key pathogenesis being the deficiency of the spleen and kidney. Only when the spleen and kidney are in harmony and the basis of mutual nourishment in successive days can the essence be abundant and the blood be replenished. Therefore, pottery pot drink was used as the basis for the differentiation and treatment of IDA syndrome. The formula mainly consists of Radix Astragalus, cooked Rehmannia, Angelica, Radix Paeoniae, Chuanxiongxi, Radix pseudostellariae, Tuckahoe, Radix paeoniae, stir-fried Licorice, jujube, Radix asparaginae, Wolfberry, jujube kernel, Chinese Yam, Ejiao, longan meat, raspberry, Schisandra, Wumei, etc. The clinical effects are remarkable. Han et al. [40] treated blood deficiency due to Yang excess. Although blood deficiency is related to all the five viscera, it is especially closely related to spleen and kidney Yang. Therefore, the treatment was mainly based on warming and reinforcing nourishment, and Lizhong Decoction and Sini Decoction were mainly used together with blood-tonifying products to strengthen warming and tonifying spleen and kidney Yang, removing disharmony and nourishing the blood. With strong blood and Qi, transportation is smooth, the body's vitality is robust, and blood is not deficient. This can lead to growth, storage, and the alleviation of blood deficiency.

3.4 Nourishing Liver and Kidney Method

Gao [41] pointed out that the deficiency of blood in pregnancy was mainly liver-kidney Yin deficiency in the two viscera of liver and kidney. Zuogui drink was used to nourish kidney Yin and nourish liver and blood, and its drug composition was: cooked rehmannia, raw rehmannia, Wolfberry, yam, Angelica, dogwood, Poria, Moutan bark, Fructus liguensis, black lotus, Polygonum multiflorum, wheat aspartame and licorice. Xiang [42] believed that Yin deficiency of the liver and kidney was the main cause of IDA aggravation, and the clinical manifestations were usually waist and knee tenderness, five upset heat, hot flush and night sweat. Therefore, ejiao, turtle shell were commonly used to nourish Yin and blood, antler gum, Zihezi and achyranthus were commonly used to nourish liver and kidney, filling essence, generating blood, and nourishing wood with water, effectively improving patients' clinical symptoms and correcting IDA.

4. The Status of Treating Iron Deficiency Anemia During Pregnancy with Both Chinese and Western Medicine.

4.1 Traditional Chinese Medicine, Combined with Western Medicine's Basic Treatment.

He et al. [43] selected 48 rats to replicate the iron deficiency anemia (IDA) model using low iron feed combined with regular bloodletting. They randomly divided these rats into four groups: the model group (without medication), the ferrous succinate group, the angelica blood-supplementing decoction group, and the combined group (iron succinate + angelica blood-supplementing decoction). The rats in each group were then gavaged with the corresponding drugs. The results showed that compared with other groups, the levels of Hb, HCT, RBC, MCHC, and iron content in the serum and organs of rats in the combined group were increased and

higher than those in the other groups. He believes that IDA treatment should be based on invigorating the spleen, supplementing Qi, and blood. Danggui Buxue Tang originated from the book "Debate on Internal and External Injuries and Confusion", which states: "Tangible blood cannot be rapidly generated, and intangible qi should be rapidly solidified." It is one of the classic prescriptions in traditional Chinese medicine for replenishing qi and generating blood. In its formula, Huangqi, which is sweet and warm, is used to nourish the spleen and lungs, strengthen the muscle surface, and nourish the source of qi. It is supplemented with Danggui, which nourishes the blood and nourishing the body. Yang generates yin, and long generates blood. The medicine is simple and effective. Pharmacological studies have found that Astragaloside, contained in Astragalus, can effectively improve the hematopoietic function of the body. Angelica polysaccharide, the main active ingredient in Angelica, can form a polysaccharide-iron complex with trivalent iron and effectively promote iron absorption. Obviously, Angelica Buxue decoction can effectively cooperate with ferrous succinate to intervene and improve the symptoms of iron deficiency in IDA rats during pregnancy. Zhang [44] randomly divided 219 patients with IDA into a control group of western medicine ferrous fumarate tablets and an observation group of Western medicine combined with Chinese medicine Guipi Decoction. The results showed that the total effective rate of observation group was 99.09%, which was significantly higher than that of control group 73.39%. "The 'Neijing' states: 'When the middle burner absorbs Qi and extracts juice, it changes and becomes red, which is called blood.' Spleen deficiency and the lack of biochemical sources of Qi and blood are the main pathogenesis of this disease. Guipi Tang has the effects of nourishing Qi and blood, strengthening the spleen, and nourishing the heart. When combined with various medicines, it replenishes the heart and spleen, nourishes Qi and blood, and eliminates all symptoms. Clinical studies have shown that Guipi Tang combined with iron agents has a definite therapeutic effect on gestational IDA, and can significantly improve gastrointestinal reactions." Yang et al. [45] randomly divided 70 IDA patients during pregnancy into two groups. The control group was given an oral solution of iron protein succinate, while the observation group received a combined treatment of Western medicine and a self-prepared Yiqi and blood-supplementing ointment for 2 to 4 weeks. The results showed that the levels of Hb, RBC, MCV, MCHC, SI, and iron-related indexes in the observation group were higher than those in the control group, and the incidence of adverse pregnancy outcomes in the observation group was lower than that in the control group ($P < 0.05$). Self-prepared Yiqi Tonifying Blood Cream is derived from eight authentic recipes, including Codonopsis, Radix Astragalus, White Peony Root, Tuckahoe, Chuanxiong, Angelica, Jujube, Ginger, Ejiao, and Brown Sugar. This cream nourishes the spleen and kidney, tones the Qi and Blood, and has a beneficial effect on the treatment of anemia. Modern medical research indicates that Yiqi Tonifying Blood Cream can improve cells' ability to absorb iron, accelerate the maturation of primitive red blood cells into mature ones in the peripheral blood, thus repairing the hematopoietic mechanism of anemia patients and significantly enhancing the anemia condition in IDA patients. It is evident that the integration of traditional Chinese medicine with Western medicine offers significant

clinical benefits in the treatment of IDA during pregnancy. In promoting the culture of traditional Chinese medicine, there should be continuous innovation in closely integrating traditional Chinese and Western medical practices, drawing on each other's strengths, and jointly benefiting patients in clinical settings.

4.2 Chinese Patent Medicine Combined with Western Medicine Basic Treatment

Lv [46] divided 80 IDA patients in pregnancy into control group and observation group. The control group was given oral ferrous succinate tablets, and the observation group was treated with oral Yiqi Weixue capsule for 3 months on this basis. The results showed that anemia and iron-related indexes in the observation group were higher than those in the control group, indicating that combined Yiqi Weixue capsule on the basis of Western medicine treatment could effectively improve anemia indexes in IDA patients. Yiqi Weixue capsule is composed of jujube, astragalus and pig blood to play the effect of supplementing qi and blood. Pharmacological studies have shown that pig blood contains heme iron with stable structure, which is absorbed into human gastrointestinal tract in complete molecular form and has no obvious stimulation to gastrointestinal tract. Astragalus can promote the use of iron by the body and correct the symptoms of anemia. Zhao et al. [47] randomly divided 100 IDA patients in pregnancy into a Western medicine group and a Chinese patent medicine group. The Western medicine group was given oral sustained-release ferrous succinate tablets, while the Chinese patent medicine group was given Jianpi Shengxue granules and ferrous succinate sustained-release tablets. The results showed that the Chinese patent medicine group was superior to the Western medicine group in regulating iron metabolism and blood biochemical indices, and also reduced the occurrence of adverse pregnancy outcomes. Wu et al. [48] treated IDA with Xinxuebao capsule; the control group was given Duowei Iron oral liquid. Xinxuebao capsule was added to the control group, and continuous treatment was carried out for 4 weeks in both groups. The results showed that the total effective rate of the treatment group was 96.77%, and the levels of Hb, MCH, MCHC, and ferritin were significantly higher in the treatment group than in the control group. Wu et al. [49] divided 108 patients into an iron protein succinate oral solution group and a combination group (iron protein succinate oral solution + Shengxuebao mixture), and treated both groups for one month. The results showed that the total effective rate and the levels of HB and SI in the combination group were higher than those in the iron protein succinate oral solution group, and the incidence of adverse pregnancy outcomes in the combination group was lower than that in the iron protein succinate oral solution group ($P < 0.05$). It can be seen that proprietary Chinese medicine not only promotes the absorption of iron but also mitigates the adverse reactions caused by Western medicine. It can also be used alone or in combination, and this combined method can be widely implemented in clinical practice [50].

4.3 External Treatment of Chinese Medicine Combined with Basic Treatment of Western Medicine

Traditional treatment method originating from ancient Chinese medicine, the theoretical basis of acupoint

application lies in the holistic view of Chinese medicine, meridian theory, and the physiological effects of acupoints. The therapy achieves the goal of disease treatment through a dual mechanism: applying drugs to specific body points, exerting the effects of direct penetration and absorption of drugs, and activating the qi of meridians and collateral channels through acupuncture point stimulation to produce indirect therapeutic effects. Traditional Chinese medicine is absorbed As a directly through the skin, and less is metabolized by the liver, greatly reducing toxic side effects and adverse reactions. It is easy to operate, economical, non-invasive, and painless [51, 52]. Xia et al. [53] applied Banxia Houpu paste to Shenque, Zhongwan, Qihai, Guanyuan, and bilateral Tianshu points to treat constipation and abdominal distension caused by iron deficiency anemia (treatment group); 32 cases were included in each of the control and treatment groups, which were treated with conventional iron therapy. The results indicated that the treatment group exhibited better symptom improvement than the control group, effectively enhancing gastrointestinal function in patients. Symptoms of constipation and abdominal distension in IDA patients were alleviated, and no patients experienced discomfort. Zhou et al. [54] applied Angelica sinensis, Chuanxiong, and other drugs to Geshu and spleen acupoints in the treatment group for iron deficiency anemia, with both the control and treatment groups receiving oral iron supplementation. The research findings revealed that the treatment group had a 90% effective rate, compared to 70% in the control group. It can be seen that acupoint application is effective and reliable for IDA and its complications. In addition, TCM external treatment includes therapies such as acupuncture, moxibustion, acupoint injection, and massage, which are effective in improving iron deficiency anemia in children and non-pregnant adults. However, for the special group of pregnant women, more large-scale and multi-center randomized controlled trials are needed to verify the effectiveness, in order to provide a more precise diagnostic and treatment basis for clinical practice [55, 56].

5. Outlook

The comprehensive use of traditional Chinese and Western medicine treatment can not only reduce the adverse reactions caused by iron, but also promote the absorption and utilization of iron. It involves both internal and external treatment, giving full play to their respective advantages and improving the therapeutic effect. It can be seen that the treatment of iron deficiency anemia during pregnancy is the future direction of development. However, there are still some problems in the current research, such as insufficient evidence in evidence-based medicine and imperfect research designs. Therefore, future research should focus on improving the quality of research, enhancing the evidence base of evidence-based medicine, optimizing study designs, and further exploring the specific methods and mechanisms of integrated Chinese and Western medicine in treating iron deficiency anemia during pregnancy. This will provide more effective treatment programs for clinical practice.

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