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Diagnosis and Treatment of Ferropenic Anemia in Primary Care in Spain

Germán Las Heras Manso*

Hematology and Hemotherapy Service, Parc Sanitari Sant Joan de Déu, Sant Boi, Barcelona, Barcelona, Spain.
Corresponding author. Email address: german.lasheras@sjd.es

Abstract: Background and objective: Iron deficiency anemia is a frequent cause of consultation in routine medical practice. Knowing how it is diagnosed and treated in Primary Care can allow us to detect if there is any area for improvement. Method: Descriptive multicenter survey-type study with 12 questions to find out the aspects of greater variability in the management of iron deficiency anemia. The population under study are physicians from Primary Care Centers nationwide who treat these patients. Results: 732 physicians answered the form and 51.8% consider iron deficiency anemia a serious disease. To make the diagnosis, 80.7% check the ferritin and only 27.2% check the transferrin saturation index (TSI). 71.6% perform control tests every three months, 57.9% prescribe iron only for three months, and 47% end treatment when Hb normalizes. When the patient is referred, the majority do so to the digestive service, followed by hematology, internal medicine, and gynecology. Conclusions: Despite the fact that almost 52% of those surveyed consider iron deficiency anemia a serious disease and that ferritin is the most useful biochemical determination for its diagnosis, around 20% do not use it. On the hand, the TSI, which can often help distinguish iron deficiency anemia from inflammatory anemia, is only requested by slightly more than 27%, which can lead to diagnostic errors. On the other hand, on some occasions, the treatment is insufficient, since the majority treat the patients for only 3 months and 47% finish the treatment when the Hb normalizes without taking into account the ferritin result. Although the diagnosis and treatment of iron deficiency anemia in Primary Care has improved, it is likely that many patients would benefit from greater use of ferritin and TSI and from longer-lasting treatments.

Key words: iron deficiency anemia; iron deficiency; ferritin; primary care

1. Introduction

Iron deficiency is the most common nutritional deficiency in the world, both in developing and industrialized countries. Iron deficiency anemia accounts for over 50% of all anemia cases. Their impact on physical, psychological development, and job performance is an important issue in public health and a reason for frequent consultation in routine medical practice [1].

It can occur in all ages, but its prevalence is higher in women of childbearing age due to iron loss through menstruation; and in children, where the amount of iron in food is often not sufficient to meet the demand. A 2019 World Health Organization report estimated that 39.8% of children and 29.9% of non-pregnant women had anemia [2]. A 2016 meta-analysis described that 25% of children and 37% of women had iron deficiency anemia [3].

Iron deficiency anemia is caused by a negative balance between iron intake and iron needs, so anamnesis is essential. It can be produced by a deficit of intake (iron deficient or strict vegetarian diet), absorption problems (inflammatory bowel diseases, bariatric surgery, malabsorption syndrome in intestinal or gastric resection), increased demand (pregnancy, lactation, growth, continuous intense exercise) or due to increased losses, whether digestive or menstrual, without forgetting regular blood donors (250 mg of iron are lost in each donation) [4] and the use of gastrolesive drugs, such as non-steroidal anti-inflammatory drugs or aspirin.

The diagnosis of iron deficiency anemia is usually easily made through blood tests that detect low/non reproductive hypochromic small cell anemia (normal or reduced reticulocyte count), iron metabolism studies that detect iron, ferritin, and low transferrin saturation index, and evaluation of acute phase reactants. Ferritin is the preferred parameter for diagnosing iron deficiency anemia because it is associated with iron deposition in the body provided there is no inflammation, as its behavior as an acute phase reactant may mask iron deficiency anemia in the process of chronic disease [5].

Once diagnosed, an attempt should be made to identify the cause of the iron deficiency, since it is associated with significant morbidity and mortality, and, whenever possible, to correct the anemia by iron therapy [5, 6]. The route of administration, the drug used and the duration of treatment will depend on the severity of the anemia.

Surveys in the field of health are useful tools for obtaining information on different aspects of diseases, including the diagnosis and treatment habits of doctors serving affected populations. The purpose of this survey is to describe how primary healthcare in Spain diagnoses and treats iron deficiency anemia, which may help identify any areas for improvement.

2. Design and Methods

This was a descriptive multicenter survey-type study, with closed response options: yes or no, or multiple choice answers, including the usual alternatives in clinical practice, using a Likert scale when considered necessary.

A scientific coordinator created a questionnaire with 12 questions that allowed us to know the study population and identify the key aspects in the management of iron deficiency anemia and those with the greatest variability in the practice of the care process. A limited number of questions were chosen so that the survey could be completed in a few minutes.

The questionnaire included some initial questions about the investigator to better understand the study population, which consisted of physicians working in Primary Care Centers (PCC), distributed throughout the country, who were responsible for the care of patients with iron deficiency and who agreed to participate in the study.

The reference population was all the inhabitants attended in all the PCCs that exist in Spain. For this purpose, a random selection of the PCCs was made, to which the study documentation was sent by e-mail or standard mail, together with a randomized number for access to a web site designed exclusively for this study. The participating PCCs chose the physician who completed the questionnaire. In order to access the survey, the physician registered on the website, using the randomized number assigned to him or her and a password of his or her choice was generated. In this way, it is impossible to know which physician completed the survey and in which PCC he/she works.

The method used for sample predetermination was the 95% confidence interval for a proportion from a finite population. To obtain a 95% confidence interval and a precision of ± 5%, the final sample size was estimated at 340 respondents, which was increased to 400, calculating losses of 15%.

The surveys were completed between May 2 and September 15, 2020. For each participant, 5 professional-dependent variables and 12 clinical practice-dependent variables were collected.

The first were: age expressed in years completed, gender as a dichotomous variable, male or female, the autonomous

community where they practice, and the area of practice to know the size of the population where they work. Here, it is divided into three categories based on the number of residents: rural (< 5,000 residents), semi urban (5,000 - 2,0000 residents), and urban (> 20,000 residents), and finally the average daily care pressure mentioned by professionals themselves.

To learn about the physician's usual practice in the management of iron deficiency, we included different clinical practice variables on diagnosis, risk stratification, type and time of treatment, follow-up and referral of patients.

The questions with the different options were as follows:

(1) Do you think the diagnosis of iron deficiency anemia is a serious disease? Yes or no.

(2) What tests do they require to diagnose iron deficiency anemia? Hb, ferritin, TSI and reticulocyte count with multiple response option.

(3) To evaluate the ferritin results of the analysis: Have you considered the reference values of the laboratory conducting the analysis? They use fixed values (< 15 µg/l for premenopausal women and < 30 µg/l for men and postmenopausal women)? Or other reference values different from the above?

(4) How often do you conduct comparative analysis on these patients? Every month, every three months, every six months, or every six months or more.

(5) How long does the recipe for iron take? Three months, six months, over six months, or opening a certain number of iron boxes.

(6) When does iron therapy end? When HB is normalized, when ferritin is normalized, when TSI > 20%, or a certain number of iron boxes are formulated separately based on these values.

(7) What do you do when a patient does not fully respond to treatment? Ask the patient if they have indeed taken iron, switch the medication to one containing more elemental iron, or transfer it to a reference center for intravenous iron injection.

(8) When you decide to refer a patient for learning? Which other specialist would you send it to? Gastroenterology, internal medicine, gynecology, hematology or other majors.

(9) Is it fixed on the amount of elemental iron in your formula's iron preparation? Always, forever, sometimes.

(10) Is the iron in your formula iron or ferrous? Yes or no.

(11) What dosage form do you prefer to use? Capsules, soluble tablets, sachets, coated tablets or drinkable vials.

(12) Have you considered the differences between these different oral iron preparations? Yes or no.

3. Results

Seven hundred and thirty-two doctors, each from a different PCC, answered the web-based survey form. 69% were between 40 and 60 years old, and 50.7% were women. Women were slightly younger than men: 61.8% of women were < 50 years old, while 54% of men were > 50 years old ($p < 0.001$). The distribution of participants by autonomous community is shown in Table 1.

Table 1. Distribution of participants by autonomous communities

Autonomous community	N (%)
Andalusia	27 (3.7%)
Aragon	25 (3.4%)
Canary Islands	71 (9.7%)
Cantabria	11 (1.5%)

Autonomous community	N (%)
Castile and Leon	25 (3.4%)
Castilla - La Mancha	64 (8.7%)
Catalonia	153 (20.9%)
Valencian Community	81 (11.1%)
Extremadura	47 (6.4%)
Galicia	26 (3.6%)
Madrid	160 (21.9%)
Murcia	15 (2.0%)
Basque Country	27 (3.7%)
Total	732 (100.0%)

Physicians from 13 Autonomous Communities responded and more than half of the participants (53.9%) belonged to three Autonomous Communities: Madrid, Catalonia and the Community of Valencia. A total of 62.7% practiced in urban areas, 22.1% in semi-urban areas and 15.2% in rural areas. By sex, women work more frequently in urban areas (66.9% versus 58.5%). This difference is statistically significant ($p = 0.009$).

Regarding the average number of patients seen in a normal day: the majority (54.9%) visit between 31 and 50 patients per day, 26.9% more than 50 patients and 18.2% less than 30 patients. Regarding the first question: 51.8% of the respondents consider iron deficiency anemia to be a serious disease. Each of the answers on clinical variables was assessed according to the physician's opinion on whether or not iron deficiency anemia was a serious disease.

In relation to the second question, to make the diagnosis of iron deficiency anemia, 87.7% check Hb, 80.7% check ferritin determination, 27.2% request TSI and 18.2% reticulocyte count. Physicians who consider iron deficiency anemia to be a serious disease request TSI in a much higher proportion: 34.56% versus 19.26%. These differences are statistically significant.

The results of question 3, on which ferritin reference values are used to determine whether or not the patient is iron deficient, are shown in Figure 1. There were no differences between those who consider iron deficiency anemia to be a serious disease or not.

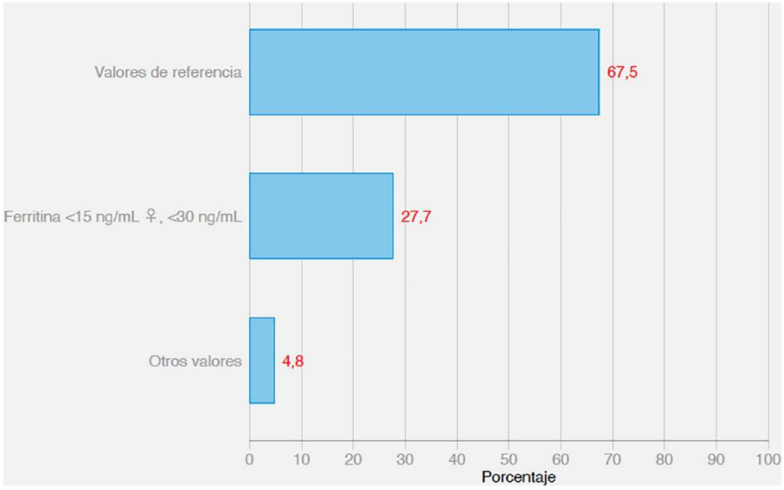

Figure 1. Reference values for ferritin result.

With regard to question 4, how often do they perform control tests in a patient diagnosed with iron deficiency anemia: 71.6% answered that they perform control tests every three months, 22% every six months, 5.3% every month and 1.1% every more than six months (Figure 2). Those who consider iron deficiency anemia to be a serious disease perform more controls in the first month ($p < 0.05$) (7.7% versus 2.8%).

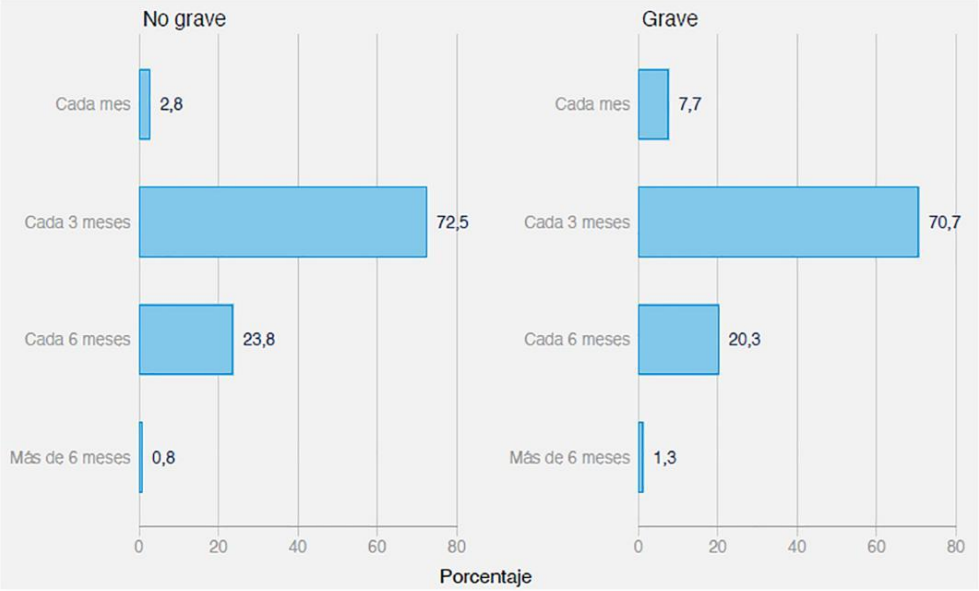

Figure 2. Frequency of control tests as a function of severity.

The results of question 5 on how long they prescribe iron are shown in Figure 3, 57.9% prescribe iron for three months, 33.9% for more than six months, 4.5% prescribe a fixed number of boxes of iron and 3.7% for more than six months. Regarding the consideration of severity, no differences were detected between the two groups.

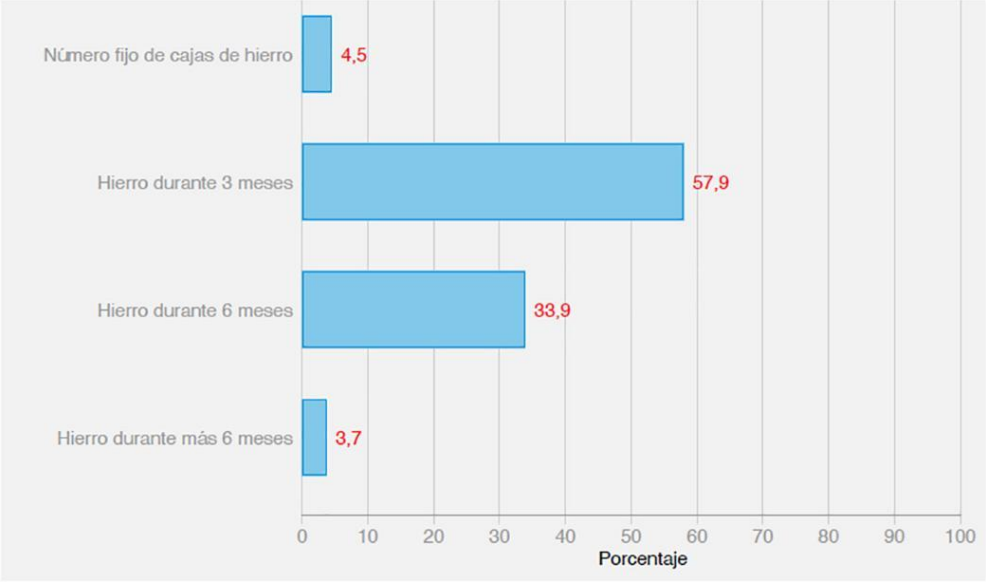

Figure 3. Duration of treatment.

In relation to question 6, as can be seen in Figure 4, almost half of the respondents value Hb and only 45% look at ferritin values to finalize treatment. Those who consider iron deficiency anemia a serious disease use the TSI result in greater proportion to withdraw medication ($p < 0.05$).

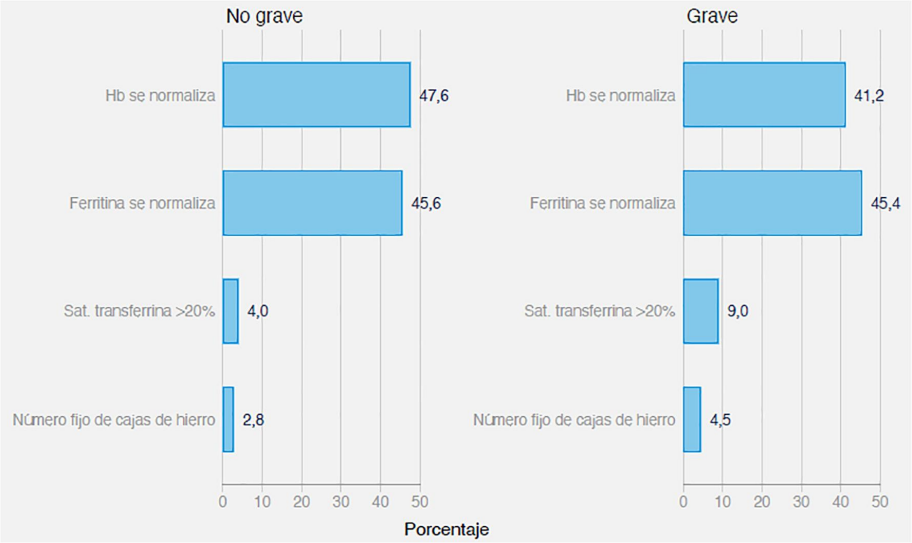

Figure 4. When treatment ends according to severity.

In question 7, regarding what to do when the patient does not respond adequately to the iron prescribed, 85% ask the patient if he/she has really taken it, 49.18% change to a preparation with more elemental iron and 15.98% refer the patient to the referral center to administer IV iron. No differences were detected between those who consider iron deficiency anemia to be a serious disease and those who do not.

In relation to question 8, when the patient is referred for study, most patients are referred to the digestive service, followed by hematology, internal medicine and gynecology. Those who consider iron deficiency anemia to be serious refer more often to internal medicine and those who do not consider it to be serious refer more often to hematology.

In question 9, regarding whether they take into account the amount of elemental iron in the iron preparation they prescribe, 69.5% do take it into account, 2.9% never consider it, and 27.6% only consider it on some occasions. Those who consider iron deficiency anemia a serious disease take it into account to a greater extent ($p < 0.05$).

Regarding question 10, concerning the iron preparation they prescribe, 92.5% of physicians take into account whether the iron they prescribe is ferric or ferrous. However, those who consider iron deficiency anemia a serious disease take this factor into account much more significantly, as shown in Figure 5 ($p < 0.05$).

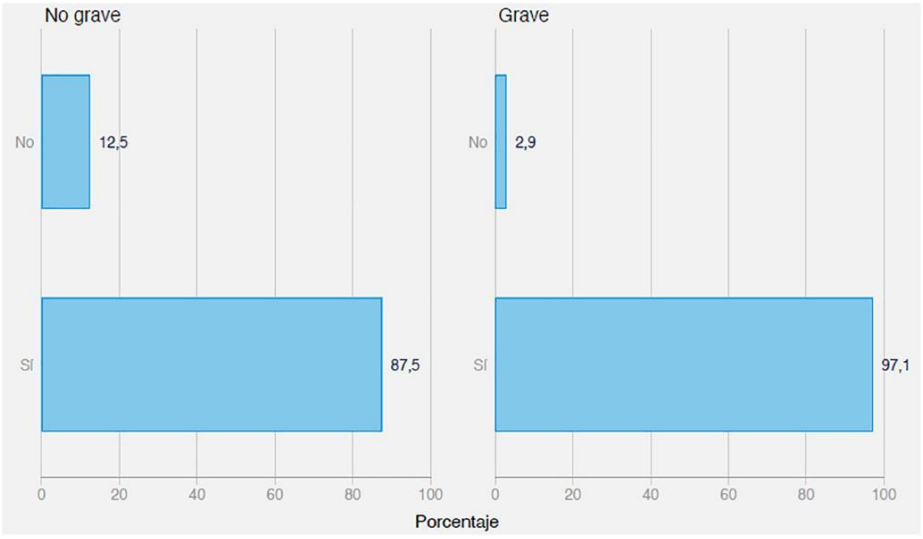

Figure 5. Assesses whether the iron you are prescribing is ferric or ferrous.

In question 11, on the dosage form they prefer to use: the preferred presentation is capsules, followed by tablets. Those who consider iron deficiency anemia a serious disease prefer sachets and capsules, and those who do not consider it a serious disease prefer coated tablets. The differences are significant ($p < 0.05$).

Regarding question 12, 92% of the respondents take into account the differences between the different oral iron formulations. This percentage increases to 95.5% among those who consider iron deficiency anemia as a serious disease.

4. Discussion

Iron deficiency anemia is the most common type of anemia in the world and for this reason, both iron deficiency and iron deficiency anemia are a global health problem and a frequent cause of consultation in medical practice [1-4].

The vast majority of physicians who answered the survey work in urban (62.7%) or semi-urban (22.1%) settings, with very little participation from rural settings. Therefore, the results are not representative of the rural setting.

In this study, slightly more than half of the participating physicians (51.8%) considered iron deficiency anemia to be a serious disease, as it may be the first warning sign of intestinal tract neoplasia [7-9]. In adult men and menopausal women, gastrointestinal bleeding is the most frequent cause of iron deficiency anemia (the second in premenopausal women) and thus, in 62% of patients undergoing endoscopy for iron deficiency anemia, potentially bleeding benign lesions are found, in 19% peptic ulcer and in 11% a colorectal neoplasm [10, 11]. For this reason, some authors recommend performing digestive endoscopy in this population when there is no clear alternative cause, particularly if the Hb level is < 10 g/dL, if digestive symptoms are present, or if there is a family history of colorectal neoplasia [7, 8, 10]. However, in men under 50 years of age and in premenopausal women in the absence of symptoms, the yield of digestive endoscopy is very low (colon neoplasia in 0.8% of men and no cases in women) [12], so that in these patients it is acceptable to initiate treatment with oral iron without performing a digestive study, but evaluating the response after 1-2 months in case it is not adequate [7]. Oral iron can also be started without further examinations in subgroups of patients with a known tendency to iron deficiency anemia, such as pregnant women, athletes or regular blood donors [7].

Some authors recommend, if there is no clear triggering cause, ruling out celiac disease, autoimmune gastritis or Helicobacter pylori infection [10] and if menstrual losses are abundant, requesting a study of von Willebrand's disease [13]. Nevertheless, an etiological diagnosis is not possible in 30% of patients [14].

To diagnose iron deficiency anemia, ferritin determination is the most sensitive, specific and cost-effective laboratory test [8, 15, 16]. In this study, 80.7% of physicians request it, which implies that almost 20% (19.3%) recommend starting treatment with oral iron based only on the Hb result, which can lead to diagnostic errors or insufficient treatment [17].

However, since ferritin is an acute phase reactant, it is not always easy to establish the ferritin threshold below which the patient is iron deficient, especially when, in addition to iron deficiency, the patient has a chronic or inflammatory disorder that may be the cause of anemia. The coexistence of both types of anemia occurs in 20 to 85% of patients with inflammatory anemia and complicates the diagnosis [4, 6, 18]. In these cases, in addition to acute phase reactant parameters such as CRP, fibrinogen or ESR, the determination of the plasma level of the soluble transferrin receptor, which is not modified by inflammatory processes, could be useful, although it is not a test that is routinely performed in all laboratories [6, 9, 16, 19]. Ferritin values > 100 μg/L rule out iron deficiency and < 15 μg/L confirm it with a specificity of 99%, but with a sensitivity of only 59%.

In this sense, a ferritin value of 45 μg/L has been suggested as the limit for an optimal relationship between sensitivity (85%) and specificity (92%). Thus, if the ferritin result is between 45 and 100 μg/L, it is difficult to discern whether it represents actual iron deposition levels or is elevated due to a systemic inflammatory process. There is no agreement on which ferritin values should be used: in cases of inflammation and in some obstetric bleeding management guidelines, it is

suggested to consider iron deficiency (ferropenia) below 30 μg/L, since the sensitivity is 92% and specificity 98% [7, 10, 16, 17, 20]; if there is neoplasia or infection, below 50 μg/L; in cases of inflammatory bowel disease, if ferritin is < 100 μg/L [15, 22]; in patients with heart failure, if it is between 100 and 300 μg/L with a TSI < 20% [10, 15, 23]; and in cases of chronic kidney disease, if it is < 500 μg/L with a TSI < 30% .

In this study, most of the participating physicians (67.5%) used the reference values of the laboratory where the analysis was performed and only 27.7% considered the patient to be iron deficient if the ferritin determination was < 15 μg/L in premenopausal women and < 30 μg/L in men and menopausal women. Adopting laboratory reference values, in patients with comorbidities, may cause patients with iron deficiency to go undiagnosed or even referred to other specialists.

An accessible test that can also aid in the diagnosis is the determination of TSI. Although TSI also decreases in inflammatory anemia, when it is < 16%, it correlates with insufficient iron for normal erythropoiesis. As already mentioned, the same occurs if TSI is < 20% in cases of heart failure and < 30% if chronic renal failure is present [8, 15, 17, 18, 23]. Despite this, in this study, only 27.2% of respondents requested IST. Physicians who consider iron deficiency anemia to be a serious disease request it in a higher proportion.

In relation to the treatment of iron deficiency anemia, oral iron administration is the most cost-effective option. It is best taken on an empty stomach and with vitamin C, which increases absorption by 30% [16]. Absorption inhibitors such as dairy products, tea or coffee should be avoided, as well as drugs that reduce gastric acidity such as antacids [5]. When oral iron treatment is started, reticulocytosis appears from the fourth day, and Hb starts to improve from the second week and increases by 1 g/dL after two or three weeks. A minimum of three to six months of treatment is required to normalize ferritin and replenish iron stores, although depending on the intensity of iron deficiency, more time may be needed [5-7, 15, 24]. A frequent cause of non-response is due to short duration of treatment [15]. In fact, there are many patients who require chronic oral iron therapy, including all those with chronic intestinal bleeding, hypermenorrhea, inflammatory bowel disease, malabsorption, blood donors and endurance athletes. It is therefore recommended, once treatment is started, to check in 1-2 months that the Hb improves and once the target ferritin is reached, to repeat the blood count with the parameters of iron metabolism at 3-6 months to assess whether they need to continue iron treatment and to evaluate at what dose, by what route of administration and how often [4-6].

In this study, the majority of doctors (57.9%) prescribed iron for only 3 months and only 33.9% prescribed it for more than 6 months. 71.6% performed control tests at 3 months and 22% at 6 months. 44.3% discontinued treatment when Hb normalized, without assessing ferritin levels. 45.5% discontinued when ferritin normalized and only 6% discontinued when TSI was > 20%. Withdrawing treatment by assessing only Hb without knowing whether ferritin had recovered may result in insufficient treatment duration, since ferritin is one of the first parameters to decrease and the last to normalize. The same may occur when iron is stopped if TSI is still below 20%.

When the patient does not respond adequately to the iron that has been prescribed, 85% of physicians question the patient about whether he or she has actually taken it, 49.18% change the patient to a preparation with more elemental iron, and 15.98% refer the patient to the reference center for IV iron administration. No differences were detected between those who consider iron deficiency anemia to be a serious disease or not.

A frequent cause of therapeutic noncompliance, which can reach 40%, is the high frequency of adverse effects, especially gastrointestinal, which range from 3.7 to 43.3% [6, 25]. In these cases, spacing the intake every 48 hours has proven to be useful, since it prevents the absorption of iron by the enterocyte from becoming saturated and can be a good initial strategy for iron deficiency patients without anemia or with mild anemia [6-8, 10, 26, 27, 28].

When it comes to referring patients, most of the physicians surveyed refer them more frequently to gastroenterologists, who specialize in endoscopic examinations, followed by hematology and internal medicine referrals, which are likely to initiate intravenous iron therapy or rule out von Willebrand disease [7, 13]. Fourth, they are referred to gynecology, possibly for treatment to control hypermenorrhea [7]. It is noteworthy that those who consider iron deficiency anemia to be serious are more likely to refer to internal medicine when it should be gastroenterology, and those who do not consider it serious are more likely to refer to hematology, possibly to start IV iron.

Assessing the amount of elemental iron contained in the administered iron preparation is a very important aspect. Some authors recommend doses of 100-200 mg of elemental iron per day for an adult [15]. In this study, only 69.5% of physicians take into account the amount of elemental iron in the preparation, 2.9% never assess it and 27.6% only occasionally. Those who consider iron deficiency anemia a serious disease review it to a greater extent ($p < 0.05$).

Regarding the preferred dosage form: the preferred presentation is capsules, followed by tablets. Those who consider iron deficiency anaemia a serious disease prefer sachets and capsules, and those who do not consider it serious prefer coated tablets ($p < 0.05$). 92% take into account the differences between the different oral iron formulations. This percentage increases to 95.5% among those who consider iron deficiency anaemia a serious disease.

5. Conclusions

Although almost 52% of respondents consider iron deficiency anaemia to be a serious disease and ferritin is the most useful biochemical test for its diagnosis, around 20% do not use it. Furthermore, the TSI, which can often help distinguish iron deficiency anaemia from inflammatory anaemia, is requested by only a little over 27%, which can lead to diagnostic errors. Furthermore, treatment is sometimes insufficient, since most patients are treated for only 3 months and 47% end treatment when Hb normalizes without taking into account the ferritin result. Although there has been improvement in the diagnosis and treatment of iron deficiency anaemia in primary care, it is likely that many patients would benefit from greater use of ferritin, TSI and longer-term treatments.

Ethical Responsibilities

This article is based on the results of a survey. It does not include patients or drug brands. It only includes the usual way in which each participating physician diagnoses and treats iron deficiency anaemia. The physicians participated in the survey anonymously out of their own interest in completing it. The results obtained are analysed globally and anonymously. This project was approved by the Research Ethics Committee of the Fundació Sant Joan de Déu (PIC-203-20).

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Declaration

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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