



DOI: 10.4274/haseki.galenos.2026.72692

Med Bull Haseki 2026;64(3):176-185

Side Effects and Treatment Discontinuation in Women Receiving Oral Iron Therapy: A Cross-Sectional Study

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Abstract

Aim: Iron deficiency anemia remains a common global health problem, particularly affecting women owing to reproductive and nutritional factors. This study aims to assess the use of iron preparations, their side-effect profiles, and their impact on treatment adherence among women in Türkiye.

Methods: This study was designed as a cross-sectional analytical study between October 1 and November 30, 2023. A total of 270 female patients receiving iron replacement therapy for at least one month were included in the study. A structured 20-item questionnaire was used to collect data on demographic characteristics, iron preparations, side effects, and treatment adherence. Data were analyzed using descriptive statistics, chi-square tests, t-tests, and binary logistic regression to identify predictors of treatment discontinuation.

Results: Nausea was the most frequently reported cause of medication discontinuation (84.0%) and of switching (73.4%). Iron (III) polymaltose complex was associated with the highest rates of side effects (55.6% reported dyspeptic complaints) and treatment discontinuation (88.9%). The tablet formulation substantially increased the risk of treatment discontinuation by approximately ninefold overall and by about 5.6 fold due to side effects. Each additional year of age increased the odds of discontinuation by 10.4% (odds ratio 1.104; 95% confidence interval 1.062-1.146; $p < 0.001$). Non pregnant women experienced higher rates of side effects, treatment discontinuation (47.2% vs. 30.9%), and medication changes (38.9% vs. 25.3%) than pregnant women ($p = 0.007$; $p = 0.018$).

Conclusion: These findings support the need for personalized treatment strategies that consider factors such as age, pregnancy status, and formulation type to improve adherence and minimize treatment discontinuation.

Keywords: Anemia, iron-deficiency, iron, medication adherence, pregnancy, treatment outcome

Introduction

Iron deficiency anemia (IDA) affects more than 1.2 billion people worldwide (1). Due to factors such as pregnancy and related conditions, menstrual blood loss, insufficient dietary intake, and nutritional imbalance, women are at particularly high risk (2). During pregnancy, the demand for iron increases with fetal growth and peaks in the third trimester, a physiological period often associated with IDA (3).

The primary goals in the management of IDA anemia are to identify and eliminate the underlying cause, administer an effective treatment for an adequate duration, and monitor the response to therapy. Oral iron therapy remains the basis of treatment for most patients with IDA. However, both patient- and supplement-related factors must be considered to ensure optimal iron replacement. These include underlying pathological conditions, severity of anemia, urgency for hemoglobin increase, tolerance to previous treatments, treatment

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Received: 04.09.2025 **Accepted:** 24.01.2026 **Epub:** 31.03.2026

Cite this article as: Altun Bozkurt Z, Kinaci Gumuscubuk Y, Simsek E, Dagcioglu BF, Yilmaz Cakmak N. Side effects and treatment discontinuation in women receiving oral iron therapy: a cross-sectional study. Med Bull Haseki. 2026;64(3):176-185



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resistance, history of allergic reactions, cost of medication, and potential side effects (4). For patients who cannot tolerate or do not respond to oral iron or in certain clinical situations, intravenous (IV) administration is the preferred route (5). However, IV iron therapy is associated with higher costs, the need for infusion facilities, and a low risk of hypersensitivity reactions. These factors limit its widespread use, particularly in low-income countries (6).

Although ferrous sulfate is considered the gold standard for oral iron therapy, iron preparations commonly contain one of three iron salts: ferrous sulfate, ferrous gluconate, or ferrous fumarate (7). The bioavailability of ferric iron salts is lower than that of ferrous iron salts, limiting their oral use (8). These advantages are considered when prescribing iron preparations.

One of the greatest challenges of oral iron therapy is nausea and epigastric discomfort that appears within one to two hours after ingestion. These symptoms contribute to poor patient compliance and can trigger complaints such as indigestion, nausea, vomiting, abdominal pain, constipation, and diarrhea, which are due to the oxidative effects of iron on the GI mucosa (9). These side effects are generally dose-dependent and reflect inherent properties of the iron regulatory system, which prevents long-term iron overload (9,10). Gastrointestinal (GI) side effects caused by iron therapy adversely affect the patient's health, disrupting both physiological and psychological well-being. Consequently, patients often discontinue oral iron treatment prematurely or continue therapy with a different medication or a modified treatment regimen.

We hypothesized that, in women receiving iron therapy, particularly those using tablet formulations, side effects and discontinuation rates would differ by drug formulation and that factors such as age and pregnancy status would significantly influence treatment adherence.

Despite awareness of the prevalence of IDA, which adversely affects women's health, it is believed that insufficient attention is paid to monitoring treatment in patients and pregnant women who receive prophylactic iron. Therefore, this study aimed to evaluate the use of iron preparations among female patients, determine the frequency and types of side effects, identify reasons for drug discontinuation or switching, and examine factors affecting treatment adherence.

Materials and Methods

Compliance with Ethical Standards

The local ethics committee approval was obtained from the Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 (approval no.: E1/4009/2023, date: 12.09.2023). This study was prepared in accordance with the principles of the Declaration of Helsinki.

Study Design

This study was designed as a cross-sectional analytical study between October 1 and November 30, 2023, and included female volunteers who had used iron supplements for at least one month. The study was reported in accordance with the STROBE guidelines for cross-sectional studies. Participants were recruited from the General Internal Medicine and Obstetrics and Gynecology outpatient clinics. A total of 270 women, both pregnant and non-pregnant, were included. Participation was voluntary, and data were collected through face-to-face interviews using a structured questionnaire. Informed consent was obtained from all participants. Exclusion criteria included refusal to participate, age under 18 years, male sex, and use of iron supplements for less than one month (Figure 1).

The researcher developed a 20-item questionnaire covering the participants' sociodemographic characteristics, reasons for iron supplement use, duration of use, habits, method of supplement use, experienced side effects, reasons for discontinuing treatment, and changes in medication. Treatment discontinuation was characterized as the patient-reported cessation of iron therapy prior to the physician-recommended duration. Discontinuation owing to side effects was defined as cessation explicitly linked to adverse consequences.

Statistical Analysis

Data were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). For descriptive statistics, frequencies, percentages, mean \pm standard deviation, minimum and maximum, median, and interquartile range (Q1-Q3) were reported. The normality of continuous data was evaluated using the Kolmogorov-Smirnov test, supplemented by visual examination of histograms and Q-Q plots. Student's t-test was used to compare continuous data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Binary logistic regression analysis was used to determine factors influencing drug discontinuation in patients receiving iron therapy and to predict which individuals would discontinue treatment because of side effects. In the first analysis, the dependent variable was treatment discontinuation (dropout), coded as 0= not discontinued and 1= discontinued. Variables with $p < 0.10$ in univariate analysis were included in the multivariate model. Independent variables included age, education level (ordinal), drug form, and active-ingredient group. Multicollinearity was assessed using variance inflation factor (VIF); variables with $VIF > 5$ were excluded.

In the second analysis, the dependent variable was whether the patient discontinued iron therapy due to side effects. The independent variables were the same as those

Patient Selection Flowchart

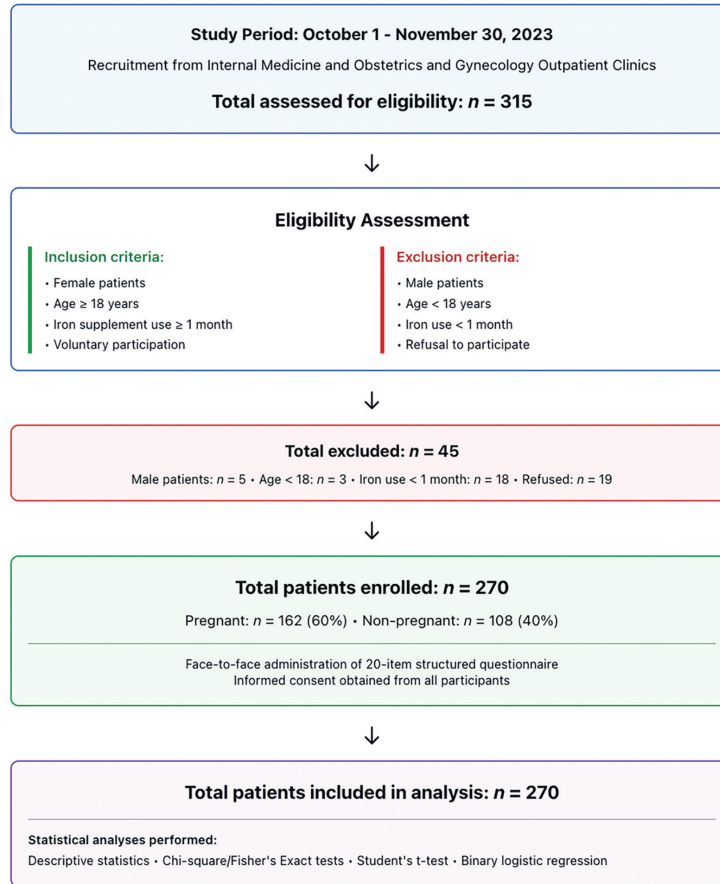


Figure 1. Flowchart of study

used in the previous analysis. Model validity was assessed using the Hosmer-Lemeshow goodness-of-fit test; explanatory power was evaluated using the Nagelkerke R-squared; and effects of variables were estimated using odds ratios (ORs) [Exp(B)] with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

Results

A total of 270 female patients receiving iron replacement therapy were included in the study. On average, patients used iron supplements for 3.59 ± 1.78 months. The vast majority of the participants (95.6%) used the supplement in tablet form. The distribution of sociodemographic characteristics and selected features related to iron supplement use among the patients is summarized in Table 1.

When asked about the side effects of the iron supplements they used, the most commonly reported side effect was nausea (35.9%), followed by constipation (19.6%) (Table 2).

37.0% of patients reported discontinuing their iron medication, and 34.8% reported changing their iron treatment. Nausea was the most common reason for both medication change (73.4%) and discontinuation (84.0%). Additionally, 68.1% of patients reported side effects even after changing their medication. Details are summarized in Tables 2 and 3.

In patients who changed their medications, the rate of side effects from their previous medications was significantly higher ($p < 0.001$). The medication discontinuation rate (88.9%) among iron (III) polymaltose complex users was significantly higher than that among other complex users ($p = 0.004$). When side-effect distribution by type of iron supplement was examined, the rate of dyspeptic complaints among patients using iron (III) polymaltose complex (55.6%) was significantly higher than that for other iron preparations ($p = 0.04$). Details are summarized in Table 4.

The mean duration of medication use was higher among pregnant women (4.40) than among non-

Category	Variables	Results
1. Sociodemographic characteristics	Patient age (year) Mean ± SD (min-max)	31.36±7.74 (19-58)
	Educational status, n (%) Primary school and below Secondary school High school University Master's/doctorate	8 (3.0) 35 (13.0) 96 (35.6) 117 (43.3) 14 (5.2)
	Occupation, n (%) Housewife Healthcare worker Teacher Student Engineer Private sector Other	134 (49.6) 32 (11.8) 35 (12.9) 14 (5.1) 5 (1.8) 29 (10.7) 21 (7.7)
2. Iron supplement usage specifications	Duration of use (months) (Mean ± SD (min-max))	3.59±1.78 (1-11)
	Drug form n (%) Intravenous (IV) Tablet Drop Syrup/suspension	0 258 (95.6) 1 (0.4) 11 (4.1)
	Type of iron supplement n (%) Ferric pyrophosphate Ferrous fumarate Iron (II) sulfate Iron (II) glycine Iron (III) hydroxide polymaltose complex Iron (III) polymaltose complex	2 (0.7) 67 (24.8) 49 (18.1) 69 (25.6) 74 (27.4) 9 (3.3)
	How the medication is obtained, n (%) By prescription From a pharmacy (paid)	266 (98.5) 4 (1.5)
	Prescribing physician, n (%) Family physician Internal medicine Obstetrics and gynecology Other	85 (31.5) 72 (26.7) 111(41.1) 2 (0.7)
	Reason for using medication, n (%) Anemia Pregnancy Weakness Hair loss Nail deformity	103 (38.1) 162 (60.0) 3 (1.1) 1 (0.4) 1 (0.4)
	Directions for use, n (%) In the morning on an empty stomach Independent of meals On a full stomach Before bedtime 2 hours after meals	162 (60.0) 41 (15.2) 29 (10.3) 25 (9.3) 11 (4.1)
Exploratory and frequency tests were used. Data are presented as mean ± SD, median (min-max), or n (%) n: Number of participants, %: Percentage, SD: Standard deviation, min-max: Minimum-maximum		

Table 2. Distribution of side effects and related treatment outcomes

Side effect type	Side effects (n=270)	Reason for treatment discontinuation (n=100)	Reason for changing medication (n=94)	Side effects after change (n=60)
Nausea	97 (35.9%)	84 (84.0%)	69 (73.4%)	42 (70.0%)
Constipation	52 (19.2%)	24 (24.0%)	22 (23.4%)	14 (23.3%)
Diarrhea	34 (12.5%)	14 (14.0%)	10 (10.6%)	11 (18.3%)
Vomiting	14 (5.1%)	15 (15.0%)	15 (15.9%)	9 (15.0%)
Heartburn	41 (15.1%)	8 (8.0%)	5 (5.3%)	5 (8.3%)
Abdominal pain	21 (7.7%)	14 (14.0%)	8 (8.5%)	5 (8.3%)
Dyspeptic complaints	41 (15.1%)	9 (9.0%)	10 (10.6%)	9 (15.0%)
Surgery	-	1 (1.0%)	1 (1.0%)	-
Forgetfulness	-	1 (1.0%)	-	-
No results from treatment	-	-	11 (11.6%)	-

Explore and frequency test were used. Data are presented as n (%)
n: Number of participants, %: Percentage

Table 3. Medication preference, change status, and post-change side effects

Category	Subcategory/option	n	Percentage (%)
Reason for preference	Because a doctor prescribes it	217	80.4%
	Fewer side effects	47	17.4%
	Habit	2	0.7%
	No special preference	1	0.4%
	Other	3	1.1%
Medication change status	Yes	94	34.8%
	No	173	65.1%
Post-change medication form	Tablet	59	63.4%
	Intravenous (IV)	25	26.8%
	Syrup/suspension	9	9.6%
Post-change side effect status	Yes	60	68.1%
	No	28	31.8%

Explore and frequency test were used. Data are presented as n (%)
n: Number of participants

Table 4. Comparison of side effects and discontinuation rates among different iron preparations

Side effects	Assessment type	Ferric pyrophosphate	Ferrous fumarate	Iron (II) sulfate	Iron (II) glycine	Iron (III) hydroxide polymaltose	Iron (III) polymaltose	p-value
Constipation	Seen	0	9 (13.4)	5 (11.9)	20 (29.0)	17 (23.0)	1 (11.1)	0.082
	Dropout	1 (50.0)	4 (6.0)	6 (12.2)	5 (7.2)	7 (9.5)	1 (11.1)	0.319
Diarrhea	Seen	0	6 (9.0)	6 (12.2)	12 (17.4)	10 (13.5)	0	0.564
	Dropout	0	3 (4.5)	3 (6.1)	6 (8.7)	3 (4.1)	0	0.785
Nausea	Seen	1 (50.0)	26 (38.8)	19 (38.8)	16 (23.2)	30 (40.5)	5 (55.6)	0.177
	Dropout	1 (50.0)	17 (25.4)	19 (38.8)	19 (27.5)	21 (28.4)	8 (88.9)	0.004
Vomiting	Seen	0	1 (1.5)	4 (8.2)	2 (2.9)	7 (9.5)	0	0.234
	Dropout	0	2 (3.0)	2 (4.8)	5 (7.2)	6 (8.1)	2 (22.2)	0.290
Heartburn	Seen	0	11 (16.4)	7 (14.3)	11 (15.9)	12 (16.2)	0	0.825
	Dropout	0	0	1 (2.0)	5 (7.2)	1 (1.4)	2 (22.2)	0.005
Abdominal pain	Seen	0	3 (4.5)	2 (4.1)	10 (14.5)	5 (6.8)	2 (22.2)	0.119
	Dropout	1 (50.0)	3 (4.5)	3 (6.1)	3 (4.3)	3 (4.1)	1 (11.1)	0.099
Dyspepsia	Seen	0	10 (14.9)	6 (12.2)	16 (23.2)	6 (8.1)	5 (55.6)	0.004
	Dropout	1 (50.0)	2 (3.0)	2 (4.1)	2 (2.9)	2 (2.7)	0	0.115
Failure to respond to treatment	Dropout	0	3 (4.5)	3 (6.1)	3 (4.3)	6 (8.1)	0	0.858

A chi-square test or Fisher's exact test was used for categorical comparisons. p<0.05 was considered statistically significant

pregnant women (2.98) ($p < 0.001$). A higher proportion of pregnant women (35.2%) than non-pregnant women (18.5%) reported no side effects ($p = 0.003$). Medication changes were more common in non-pregnant patients (38.9%) than in pregnant patients (25.3%) ($p = 0.018$). The details are shown in Tables 5 and 6.

To examine the effects of independent variables, two logistic regression models were fitted. In the overall discontinuation model, a positive association was observed between age and discontinuation, with each one-year increase corresponding to a 10.4% higher likelihood of discontinuation (OR=1.104; 95% CI: 1.062-1.146; $p < 0.001$). In the overall treatment discontinuation model,

tablet formulation was also associated with a markedly increased risk (OR=9.033; 95% CI: 1.791-45.560; $p = 0.008$). Education level showed a borderline association (OR=1.356, $p = 0.056$), whereas the active ingredient group was not significantly associated.

In the side-effect discontinuation model, age remained significant (OR=1.082; 95% CI: 1.041-1.123; $p < 0.001$), and tablet formulation was again associated with a higher risk (OR=5.599; 95% CI: 1.581-19.829; $p = 0.008$). Education level and active ingredient group were not statistically significant ($p = 0.056$). The details are shown in Tables 7a and 7b.

Table 5. Medication use, changes, and outcomes by pregnancy status

Category	Subtitle	Non-pregnant (n=108)	Pregnant (n=162)	p-value
Drug form	Tablet/syrup/drops/IV	103 tablet (95.4%)	155 tablet (95.7%)	0.458
Prescribing department	Family physician/internal medicine/gynecology and obstetrics/other	Different	Different	<0.001
Medication usage	Eating/on a full day/other	68.5% hungry	55.3% hungry	0.067
Discontinuation status	Yes	47.2%	30.9%	0.007
Drug change status	Yes	38.9%	25.3%	0.018
Drug form after change	IV/tablet/syrup	IV 46.2%	IV 2.4%	<0.001
Side effects after change	Yes	84%	73.7%	0.235

Either the chi-square test or Fisher's exact test was used for categorical variables. Student's t-test was used for continuous variables. $p < 0.05$ was considered statistically significant
n: Number of participants, IV: Intravenous

Table 6. Analysis of side effects, discontinuation, and treatment switch by pregnancy status

Side effect type	Side effects non-pregnant/pregnant	p-value	Reason for discontinuing non-pregnant/pregnant	p-value	Reason for change non-pregnant/pregnant	p-value
Nausea	47 (43.5%)/50 (30.9%)	0.034	43 (39.8%)/42 (25.9%)	0.016	35 (32.4%)/34 (21%)	0.035
Constipation	20 (18.5%)/32 (19.8%)	0.801	16 (14.8%)/8 (4.9%)	0.005	13 (12%)/9 (5.6%)	0.056
Diarrhea	13 (12%)/21 (13%)	0.822	7 (6.5%)/8 (4.9%)	0.588	4 (3.7%)/6 (3.7%)	1.000
Vomiting	5 (5.6%)/8 (4.9%)	0.823	9 (8.3%)/8 (4.9%)	0.261	9 (8.3%)/6 (3.7%)	0.104
Heartburn	17 (15.7%)/24 (14.8%)	0.835	4 (3.7%)/5 (3.1%)	1.000	2 (1.9%)/3 (1.9%)	1.000
Abdominal pain	10 (9.3%)/12 (7.4%)	0.586	9 (8.3%)/5 (3.1%)	0.057	4 (3.7%)/4 (2.5%)	0.717
Dyspepsia	16 (14.8%)/27 (16.7%)	0.684	7 (6.5%)/2 (1.2%)	0.032	8 (7.4%)/2 (1.2%)	0.016
No side effects	20 (18.5%)/57 (35.2%)	0.003	-	-	-	-

Chi-square test or Fisher's exact test was used for categorical comparisons. $p < 0.05$ was considered statistically significant

Table 7a. Multivariate analysis of predictors for overall treatment discontinuation

Variables	OR	95% CI (lower)	95% CI (upper)	p-value
Age	1.104	1.062	1.146	<0.001
Education level	1.356	0.992	1.853	0.056
Form (oral form vs other)	9.033	1.791	45.560	0.008
Active ingredient (Fe2+ vs. other)	1.172	0.252	5.444	0.839
Active ingredient (Fe3+ vs. other)	0.835	0.475	1.467	0.530

Binary logistic regression analysis was used. $p < 0.05$ was considered statistically significant
OR: Odds ratio, CI: Confidence interval, Fe2+: Iron (II) ion, Fe3+: Iron (III) ion

Table 7b. Multivariate analysis of predictors for discontinuation due to side effects

Variables	OR	95% CI (lower)	95% CI (upper)	p-value
Age	1.082	1.041	1.123	<0.001
Education level	1.310	0.929	1.846	0.124
Form (oral form vs other)	5.599	1.581	19.829	0.008
Active ingredient (Fe2+ vs. other)	0.632	0.103	3.856	0.619
Active ingredient (Fe3+ vs. other)	0.643	0.343	1.204	0.168

Binary logistic regression analysis was used. p<0.05 was considered statistically significant
OR: Odds ratio, CI: Confidence interval, Fe2+: Iron (II) ion, Fe3+: Iron (III) ion

Discussion

According to World Health Organization data for 2023, an estimated 37% of pregnant women and 30% of women aged 15-49 years are anemic (11). Various studies conducted in Türkiye have reported anemia prevalence rates of 40-50% among women of reproductive age and 14-49% among pregnant women, with iron deficiency being the primary cause (2). These findings reveal that IDA is an important public health problem, especially among women. Therefore, in our study, we targeted women, the group most affected by IDA, and investigated their use of iron supplements.

In our study, iron supplements were most commonly used during pregnancy and for anemia. Pregnant women were better informed about iron supplementation, had a more positive attitude toward treatment for iron deficiency, and demonstrated better adherence to therapy. Data obtained from the Turkey Demographic and Health Survey (TDHS) showed that 81% of women used iron supplements during their pregnancy. According to the 2018 THDS report, 75% of women had completed at least primary school, and 26% had completed at least high school (12). In our study, 43.3% of participants were university graduates, while 35.6% were high school graduates. The distribution of education levels and employment status of women in our study was compatible with that reported in the 2018 THDS data. Moreover, the education level variable showed borderline significance in our study ($p=0.056$), indicating a tendency for higher education levels to be associated with an increased risk of discontinuation (OR=1.343).

Oral iron therapy should be attempted first when initiating treatment. Parenteral iron may be administered in cases of significant blood loss, malabsorption, or intolerance to oral iron (9,13). In our study, the vast majority of patients (95.6%) used the medication orally (tablet form). Oral treatment is preferred over other therapies due to high patient compliance, greater accessibility, and cost-effectiveness (14). Previous studies generally recommend ferrous sulfate as the first-line treatment for iron deficiency (4,9,15). In our study, when

participants were asked which iron formulation they used, the three most commonly reported formulations among both pregnant and non-pregnant individuals were iron (III)-hydroxide polymaltose complex (27.4%), iron (II)-glycine (25.6%), and ferrous fumarate (24.8%). In our sample, 41.2% of iron (III) formulations were prescribed by family physicians. The high prescription rate of iron (III) preparations in this group may indicate patients' trust in primary care and in the effective functioning of the primary healthcare system. Although side effects and treatment adherence may also play a role, further comprehensive studies are needed to clarify these findings.

Gastrointestinal side effects are the most commonly reported adverse effects of treatment. GI side effects are known to occur more frequently in patients receiving oral iron therapy compared to those receiving IV formulations. The most commonly reported side effects are GI-related, including nausea, bloating, abdominal pain, diarrhea, constipation, and black or tarry stools (11). In our study, adverse effects during treatment were observed in 79.7% of patients receiving iron (III)-hydroxide polymaltose complex, 73.9% of those receiving iron (II)-glycine, 71.4% of those receiving iron (II)-sulfate, 64.2% of those receiving ferrous fumarate, and 44.4% of those receiving iron (III)-polymaltose complex. These findings indicate that GI side effects are common among individuals receiving oral iron therapy and that the frequency of these side effects varies depending on the formulation used. When researchers attempt to determine the true incidence of GI side effects associated with oral iron therapy, limitations and inconsistencies across studies make it difficult to draw definitive conclusions (9).

One review examined data on adverse events from studies of oral iron supplementation in patients without GI disease and reported an overall incidence of adverse events of 32.3% for ferrous sulfate, 47% for ferrous fumarate, and 30.9% for ferrous gluconate (16). In a study conducted by Aydin et al. (17), they compared +2 and +3 iron preparations and found no significant differences in side effects between the two preparations. In another study conducted in our country, no difference

was observed with respect to side effects between women with IDA who were treated with iron glycine sulfate (ferrous group) and those treated with iron protein succinate (ferric group) (18). Studies also show that the polymaltose complex is better tolerated than +2 iron preparations (19,20). Unlike previous studies, in our study the rate of treatment discontinuation due to nausea was significantly higher among patients using iron (III) polymaltose complex (88.9%) than among those using other formulations. When divalent (+2) and trivalent (+3) iron preparations were compared, nausea was reported more frequently among patients receiving trivalent formulations. This finding may reflect differences in tolerability between Iron(III) hydroxide polymaltose complex and +2 formulations; however, no causal inference can be drawn. Additionally, factors such as patients' previous experiences, social background, genetic characteristics, and nutritional patterns may have influenced these results, although no causal inferences can be drawn.

In studies investigating the individual side effects of IDA treatment, the most frequently reported symptoms were constipation (12%), nausea (11%), and diarrhea (8%) (9,10). When patients in our study were asked about the side effects of iron supplements, nausea was the most common response (35.9%), followed by constipation (19.6%). When participants were categorized by pregnancy status, a higher proportion of pregnant individuals (35.2%) reported no drug-related side effects than non-pregnant individuals (18.5%).

When we examined side effects, only nausea was observed significantly more frequently in the non-pregnant group. Nausea was detected more frequently than other side effects in our study, differing from previous studies; this may be explained by the fact that 60% of the participants used iron medication on an empty stomach and that a high proportion of patients in the side-effect group (approximately 60%) were taking iron for pregnancy prophylaxis. In our study, it was not possible to determine whether the high rate of nausea was pregnancy-related or a side effect of IDA treatment. Additionally, medication changes were more frequent among non-pregnant patients (38.9%) than among pregnant patients (25.3%). In both groups, nausea was the most common side effect after medication changes (70%). Although nausea is a common complaint during pregnancy, pregnant individuals may have tolerated nausea better, or iron supplements may have aggravated pre-existing nausea. However, it is not clear whether nausea was primarily pregnancy-related or caused by treatment. Further studies in pregnant populations are needed to clarify this.

In a previous study involving 96 women with iron-deficiency anemia, 40% discontinued treatment due to

side effects, the most common being GI intolerance (21). Similarly, in our study, 37% of participants interrupted treatment; nausea was again the leading reason for interruption (84%), followed by constipation (24%) and vomiting (15%). While constipation has been reported more frequently in earlier studies, our findings suggest that patients may have been more willing to tolerate constipation than nausea (10,22). Since not all side effects led to treatment discontinuation, larger sample sizes may better identify the symptoms that most strongly influence adherence.

The GI side effects of oral iron administration are dose-related. These side effects increase when the drug is administered on an empty stomach and decrease when the drug is administered on a full stomach (4). In our study, contrary to the literature, no statistically significant association was found between side effects and patients' fasting or feeding status or the time of day (morning versus evening) of iron administration. This result may be attributed to the fact that this study was not conducted as a field survey, that the evaluation was limited to patients presenting to the outpatient clinic, and that 60% of the participants were pregnant women. Additionally, patient compliance with treatment may influence the incidence of side effects.

Previous studies suggest that elderly patients may be more sensitive to dose-dependent side effects (23). In our study, older age was associated with lower adherence and some formulations appeared less well-tolerated, which was correlated with reduced treatment compliance. Therefore, the patient's age and drug formulation should be considered in treatment planning, and better-tolerated formulations should be preferred. Additionally, recent studies report that intermittent iron administration is as effective as and better tolerated than daily administration. With this approach, treatment should be individualized, taking into account the patient's tolerability and adherence to medication (24,25).

While oral iron therapy has traditionally been the mainstay of iron deficiency treatment, its effectiveness is often compromised by poor GI absorption, adverse effects, and low treatment adherence. Consequently, IV iron is recognized as a potentially more effective and safer alternative for the treatment of IDA (26,27). In this study, age and medication form were found to be significant factors influencing the discontinuation of iron therapy. In the overall discontinuation model, tablet formulation was associated with ninefold higher odds of discontinuation (OR=9.033). In the side-effect discontinuation model, tablet formulation was also associated with an increased risk (OR=5.599). These parallel findings suggest that tablet formulations were associated with higher discontinuation rates, both overall and those driven by side effects. From

a clinical perspective, these data indicate that choosing more tolerable formulations and exploring other dosing techniques, such as alternate-day administration, may improve treatment adherence in real-world practice.

Study Limitations

This study also has several important limitations. First, the cross-sectional design only allows us to describe associations at a single point in time, and no causal inferences can be made. Second, the study was conducted in a single tertiary hospital, which may limit the generalizability of the findings to other populations. Third, subgroup sizes were particularly small for some categories, such as non-pregnant women who switched to IV treatment, thereby reducing the statistical power of the analyses. Additionally, the vast majority of participants were tablet users, meaning that the study could not provide balanced comparisons across different formulations. Moreover, data were collected using self-reported questionnaires, which may introduce recall bias. Finally, information about long-term adherence, repeated interruptions, or subsequent treatment modifications could not be obtained. These limitations should be considered when interpreting the findings, and they may partly explain differences compared with previous studies. Future research should therefore employ prospective, multicenter designs with larger and more diverse populations to better capture treatment patterns and adherence factors. Despite limitations, our study provides valuable real-world data on iron therapy in women and highlights important factors influencing treatment adherence.

Conclusion

This study makes several contributions to the existing literature. First, it provides real-world data from Türkiye, focusing specifically on women who use iron supplements, a population that is disproportionately affected by IDA. Unlike many previous reports, the present study analyzed pregnant and non-pregnant women separately, revealing distinct patterns of side effects, discontinuations, and treatment switching between these groups. Moreover, the observation that family physicians were more likely to prescribe ferric formulations provides additional insight into prescribing behaviors in primary care settings. Finally, by relying on patient-reported experiences collected through face-to-face interviews, this study highlights practical challenges to treatment adherence that may not always be captured in randomized clinical trials. To our knowledge, this is the first study from Türkiye to systematically compare pregnant and non-pregnant women in this context, thereby filling an important gap in the existing literature.

The findings indicate that both age and tablet formulation were consistently linked to treatment discontinuation. These results show how important it is to think about both the patient's age and the type of iron supplement used when planning therapy. Adapting treatment to the unique characteristics of each patient and ensuring consistent follow-up can enhance adherence and decrease the probability of treatment discontinuation.

Ethics

Ethics Committee Approval: The local ethics committee approval was obtained from the Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 (approval no.: E1/4009/2023, date: 12.09.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A.B., Concept: Z.A.B., E.Ş., B.F.D., N.Y.Ç., Design: Z.A.B., B.F.D., N.Y.Ç., Data Collection or Processing: Z.A.B., E.Ş., B.F.D., N.Y.Ç., Analysis or Interpretation: Z.A.B., Y.K.G., B.F.D., N.Y.Ç., Literature Search: Z.A.B., Y.K.G., Writing: Z.A.B., Y.K.G., N.Y.Ç.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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