

SAFETY MONITORING OF IRON SUPPLEMENTATION IN PREGNANCY: INSIGHTS FROM A CROSS-SECTIONAL STUDY

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Abstract

Iron deficiency anemia is one of the most common conditions during pregnancy and is typically managed with iron supplementation. However, iron supplements may be associated with adverse reactions that affect tolerance and treatment adherence. This study aimed to evaluate the safety of iron supplements in pregnant women with anemia by analyzing adverse reactions and factors associated with their occurrence. A cross-sectional study was conducted among 105 pregnant women with anemia who were using iron supplements. Data were collected through an anonymous self-administered questionnaire consisting of four sections: demographic and obstetric data, use of iron supplements, adverse reactions, and potential influencing factors. The intensity of adverse reactions was assessed using a 5-point Likert scale. The most frequently reported adverse reactions were nausea and constipation. Most reactions were classified as moderate in intensity. No statistically significant associations were found between the pharmaceutical form of iron and reaction intensity. Taking iron with food showed a tendency toward better tolerance, while reaction intensity varied by trimester, with lower levels observed in the third trimester. Iron supplementation during pregnancy is commonly associated with gastrointestinal adverse reactions of moderate intensity. Monitoring adverse reactions and providing appropriate clinical counselling are essential to improve tolerance and ensure the safe management of anemia during pregnancy.

Keywords: adverse reactions, drug safety, pregnancy, anemia, iron supplementation

Introduction

Pregnancy represents a unique physiological period characterized by profound hormonal, metabolic, and hematological changes that support fetal growth and prepare the maternal body for childbirth. These changes include significant adaptations in the cardiovascular, hematopoietic, and immune systems, which ensure sufficient oxygen and nutrient transfer to the fetus (Cunningham et al., 2018). Plasma volume increases by about 40–50%, accompanied by a smaller increase in erythrocyte mass, resulting in physiological hemodilution. This adaptation leads to a relative decrease in haemoglobin concentration, which may contribute to the development of anemia in pregnant women (Pavord et al., 2019). According to the World Health Organisation, anemia is diagnosed when haemoglobin levels are less than 11 g/dL (WHO, 2021). Iron deficiency is the most common cause, although other factors such as folic acid and vitamin B12 deficiency, chronic infections, and inflammatory diseases can contribute to its development (Milman, 2015).

Given the high global prevalence of anemia and the increased physiological demand for iron during pregnancy, iron supplementation remains an essential component of prenatal care. The World Health Organization recommends routine iron and folic acid supplementation for pregnant women to prevent and treat anemia (WHO, 2016). Iron supplementation can be administered in various forms, including oral preparations and intravenous therapy in cases of intolerance to oral treatment or severe anemia. Oral iron therapy is considered the first-line treatment due to its effectiveness, low cost, and favourable safety profile (Pavord et al., 2019). Although iron supplementation is essential for the management of anemia during pregnancy, its use may be associated with adverse reactions that can affect tolerability and patient adherence. These reactions may lead to treatment discontinuation or irregular use of therapy, thereby reducing the effectiveness of anemia correction (Tolkien et al., 2015). In rare cases,

excessive iron intake during pregnancy may lead to toxicity, which is associated with increased oxidative stress, gastrointestinal mucosal damage, and metabolic disturbances. High iron levels may also interfere with the absorption of other micronutrients and interact with certain medications, potentially affecting their therapeutic effectiveness (Ru et al., 2024; Kalman et al., 2025).

Monitoring adverse reactions to iron supplementation is essential to ensure an optimal balance between therapeutic benefits and potential risks. This includes identification and reporting of adverse reactions, evaluation of haematological indices, assessment of individual tolerability, identification of risk factors for intolerance, and evaluation of possible drug interactions (Pavord et al., 2019). In the context of pharmacovigilance, active monitoring of adverse reactions contributes to improving clinical practice and increasing patient safety, especially in vulnerable populations such as pregnant women (EMA, 2020). Therefore, this study aims to evaluate the safety of iron supplements in pregnant women with anemia by analyzing adverse reactions and the factors influencing their occurrence.

Material and methods

This is a descriptive, cross-sectional study conducted in Tetovo, an urban city in the western part of the Republic of North Macedonia, from June 2025 to January 2026. The study population consisted of pregnant women diagnosed with anemia who used iron supplements during pregnancy. Convenience sampling was used, with participants recruited voluntarily. A self-administered questionnaire was used to collect data. The questionnaire consisted of 20 items organized into four sections: a) demographic and obstetric characteristics; b) use of iron supplements and the mode of administration; c) adverse reactions of iron supplements; and d) potential factors influencing the occurrence and intensity of adverse reactions. A 5-point Likert scale (1 = strongly disagree to 5 = strongly agree) was used to evaluate adverse reactions and factors influencing them.

Data were coded and analyzed using IBM SPSS Statistics. Categorical variables were presented as frequencies and percentages, while Likert-scale responses were treated as ordinal variables and summarized using mean and standard deviation. Associations between influencing factors and adverse reactions were assessed using Spearman's correlation coefficient. Statistical significance was defined at $p < 0.05$.

The study was conducted in accordance with ethical principles for scientific research. Participation was voluntary, and anonymity and confidentiality of data were ensured. All data were used exclusively for academic purposes.

Results

A total of 105 pregnant women diagnosed with anemia who used iron supplements during pregnancy were included in the study.

Demographic and obstetric characteristics of study participants

Based on the data presented in Table 1, the most represented age group was 20–29 years (55.2%), followed by the 30–39 years age group (32.4%) among the study participants.

Table 1. Demographic and obstetric characteristics of study participants

Variables	Percentage
<i>Age</i>	
≤20	12.4
21–30	55.2
31–40	32.4

<i>Gestational age</i>	
I trimester	6.7
II trimester	79.0
III trimester	14.3
<i>Number of pregnancies</i>	
First pregnancy	55.2
Second pregnancy	36.2
More than two pregnancies	8.6

Most of the participants were in the second trimester of pregnancy (79.0%), while a smaller percentage were in the first and third trimesters. This distribution reflects the higher frequency of prenatal check-ups and anemia diagnosis during the second trimester, a period in which iron requirements increase and supplementation begins more often.

Regarding the number of pregnancies, more than half of the participants (55.2%) were in their first pregnancy, and only 8.6% had had more than two pregnancies. This distribution indicates that the sample is dominated by primigravidas, who may have more limited experience with supplementation during pregnancy and potentially higher susceptibility to adverse reactions.

Use of iron supplements and the mode of administration

The use of iron supplements was analyzed in terms of formulation, duration of use, and route of administration as factors that may influence the occurrence of adverse reactions. These variables are particularly important for evaluating the safety and tolerability of iron therapy during pregnancy.

Tablets were the most commonly used form of iron supplementation (42.9%), followed by syrup (34.3%) and capsules (22.9%). The dominance of the tablet form may be related to standard clinical recommendations and their wide availability. Regarding the duration of use, the majority of participants (61.0%) reported using iron supplements for 1–3 months, while 24.8% reported use for less than one month and 14.3% for more than three months (Table 2).

Table 2. Formulation of iron supplements and duration of use

Variables	Frequency	%
<i>Supplement formulation</i>		
Tablets	45	42.9
Syrup	36	34.3
Capsules	24	22.9
<i>Duration of use</i>		
<1 month	26	24.8
1–3 months	64	61.0
>3 months	15	14.3

The use of iron supplements was mainly based on a doctor's recommendation (58.1%), while 21.9% of participants started supplementation on the advice of a pharmacist and 20.0% on their own initiative. These data highlight the key role of health professionals in guiding the safe and rational use of supplements during pregnancy.

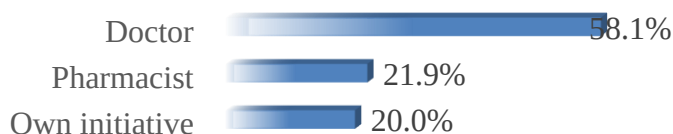


Figure 1. Source of recommendation for iron supplementation

More than half of the participants (61.0%) reported taking iron supplements with food, while 39.0% reported taking them on an empty stomach. Regarding the consumption of tea or coffee at the time of iron intake, 53.3% of participants reported consuming these beverages, 37.1% did not, and 9.5% were unsure (Table 3). These practices may influence iron absorption and, potentially, the effectiveness and tolerability of the treatment.

Table 3. Mode of iron supplementation and factors influencing absorption

Variables	Frequency	%
Mode of iron intake		
With food	41	61.0
On an empty stomach	64	39.0
Consumption of tea or coffee during iron intake		
Yes	39	37.1
No	56	53.3
Not sure	10	9.5

Prevalence and severity of adverse reactions

The prevalence of adverse reactions was determined based on the proportion of participants reporting high-intensity symptoms (Likert ≥ 4). Nausea (69.5%) and constipation (57.6%) were the most commonly reported reactions, while fewer participants reported abdominal pain (27.6%) and changes in stool colour (9.5%) (Figure 2). These findings indicate that gastrointestinal adverse reactions represent the most common form of intolerance to iron supplements in the studied population, affecting the daily activities of 48.6% of participants.

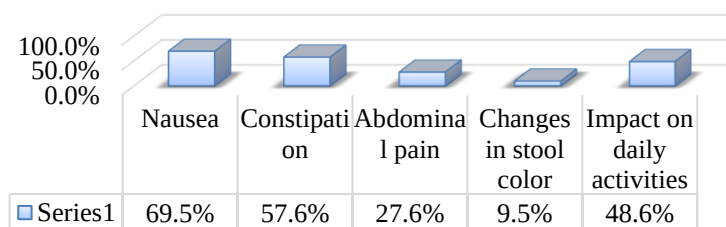


Figure 2. Prevalence of adverse reactions

The majority of participants reported a moderate intensity of adverse reactions (79.0%), while a smaller proportion reported high intensity (9.5%). This distribution suggests that adverse reactions are relatively common but are generally of moderate severity (Table 4).

Table 4. Classification of the intensity of adverse reactions among study participants

Variable	Frequency	%
Intensity of adverse reactions		
Mild (<3.0)	12	11.4
Moderate (3.1–4.0)	83	79.0
High (>4.1)	10	9.5

The intensity of adverse reactions was assessed using a reaction index, calculated as the mean of responses to five items (nausea, constipation, abdominal pain, changes in stool colour, and impact on daily activities), with higher values indicating greater intensity. The mean reaction

index was 3.58 ± 0.33 , with a median of 3.60, indicating an overall moderate intensity of adverse reactions in the studied population.

Factors influencing the intensity of adverse reactions

Mode of iron intake (with food vs. on an empty stomach)

Participants who took iron with food ($n = 64$) had a mean reaction index of 3.55, whereas those who took it on an empty stomach ($n = 41$) had a mean of 3.60. The difference was not statistically significant ($p = 0.087$).

Pharmaceutical formulation of iron supplements

No statistically significant differences in the intensity of adverse reactions were observed between different pharmaceutical formulations of iron supplements ($p = 0.628$).

Trimester of pregnancy

Differences between trimesters were statistically significant ($p < 0.001$). Higher intensity of adverse reactions was observed during the first and second trimesters, whereas lower values were reported in the third trimester.

Discussion

This study evaluated the safety and tolerability of iron supplementation in pregnant women with anemia, by analyzing the frequency, intensity and factors influencing the occurrence of adverse reactions. The findings indicate that gastrointestinal adverse reactions are common and usually moderate in intensity, while the trimester of pregnancy may affect iron tolerance. In this study, the most frequently reported reactions were nausea and constipation, followed by abdominal pain and a change in stool colour. These results are consistent with the existing literature demonstrating that oral iron supplementation is frequently associated with gastrointestinal intolerance. A systematic review by Tolkien et al. (2015) reported that constipation, nausea and abdominal pain are among the most common adverse reactions often affecting treatment adherence. Similarly, Pavord et al. (2019) highlight that gastrointestinal intolerance remains a major barrier to the management of iron deficiency anemia during pregnancy. The predominance of gastrointestinal symptoms observed in this study is also in line with research suggesting that unabsorbed iron in the gastrointestinal tract can contribute to symptoms such as nausea, constipation, and abdominal discomfort (Moretti et al., 2015).

The results showed that the majority of participants experienced reactions of moderate intensity (79.0%), while a smaller percentage reported high intensity. This suggests that, although reactions are common, they are usually manageable. Previous studies have reported similar results, showing that most pregnant women tolerate iron supplementation, despite the presence of mild to moderate gastrointestinal effects (Milman, 2015). These findings are further supported by recent evidence from a multi-centre observational clinical study by Liu et al., which emphasized the importance of systematic safety monitoring of oral iron supplementation in pregnant women. Similar to our results, Liu et al. reported that adverse reactions are relatively common but are predominantly mild to moderate in intensity and manageable with appropriate clinical oversight.

The analysis of factors influencing adverse reaction intensity in this study revealed no statistically significant differences related to the mode of iron intake (with food vs. on an empty stomach). Although dietary factors such as food intake and the consumption of tea or coffee are known to influence iron absorption, their effect on adverse reaction intensity may be limited and influenced by substantial interindividual variability (Hurrell & Egli, 2010; Milman, 2015). This variability may explain the absence of statistically significant associations observed in this study. The World Health Organisation recommends that, in case of gastrointestinal

intolerance, iron supplements can be taken with food to improve tolerance, balancing effectiveness and patient comfort (WHO, 2016). No statistically significant differences in the intensity of reactions were observed between tablets, syrup and capsules. This result suggests that the pharmaceutical formulation may not be a determining factor in iron tolerance. The literature supports this finding, indicating that gastrointestinal effects are more related to the dose of elemental iron and individual patient characteristics than to the pharmaceutical form (Milman, 2015; Tolkien et al., 2015). In contrast, statistically significant differences in adverse reaction intensity were observed across pregnancy trimesters, with higher intensity reported during the first and second trimesters. This may be related to higher gastrointestinal sensitivity and hormonal changes in the early stages of pregnancy, which may predispose women to greater intolerance of iron supplementation (Achebe & Gafter-Gvili, 2017). Cunningham et al. have reported that gastrointestinal symptoms are more pronounced in the first trimester due to hormonal changes and increased sensitivity to nausea. This may affect the tolerance of iron supplements during this period.

From a clinical and pharmacovigilance perspective, these findings highlight the importance of active monitoring of adverse reactions during iron supplementation, particularly in vulnerable populations such as pregnant women. As emphasized by both Liu et al. and the World Health Organization, systematic monitoring and patient-centred management strategies are essential for optimizing adherence, minimizing treatment discontinuation, and improving maternal outcomes (WHO, 2016).

Conclusion

Iron supplementation in pregnant women with anemia is commonly associated with gastrointestinal adverse reactions, mainly nausea and constipation, which are generally of moderate intensity and manageable in clinical practice. While pharmaceutical formulation and mode of intake were not significantly associated with reaction intensity, the trimester of pregnancy emerged as an important factor, with higher intensity observed in early pregnancy. Although most adverse reactions were not severe, they may influence treatment adherence. These findings highlight the importance of continuous monitoring, individualised counselling, and patient education to improve tolerability and ensure treatment effectiveness.

In conclusion, iron supplementation remains an important part of managing anemia during pregnancy. At the same time, an individualized and patient-focused approach, together with the active support of healthcare professionals, including pharmacists, plays a key role in improving treatment safety and achieving better clinical outcomes.

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