

COMPARATIVE BIOTECHNOLOGICAL EVALUATION OF IRON SUPPLEMENTATION MODALITIES FOR PREGNANCY-RELATED ANEMIA: INTRAVENOUS IRON SUCROSE VS. ORAL FERROUS FUMARATE AND SULFATE

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Abstract: *Pregnancy-related anemia, primarily due to iron deficiency, poses significant risks to both maternal and fetal health. Objective: The primary objective of this study is to compare the biotechnological efficacy of intravenous iron sucrose, oral ferrous fumarate, and oral ferrous sulfate in treating pregnancy-related anemia. This condition poses significant risks to maternal and fetal health. Methods: This cross-sectional study at Shalamar Hospital, Lahore (January-December 2023), involved 270 pregnant women with iron deficiency anemia. These women were randomized into three groups (90 each) receiving intravenous iron sucrose, oral ferrous fumarate, or oral ferrous sulfate. Data collected through interviews, records, and lab tests assessed hemoglobin, ferritin, and CBC at baseline, 4, 8, and 12 weeks, along with adverse effects, treatment adherence, quality of life, and biomarkers. Statistical analysis was performed using SPSS with ANOVA and Chi-square tests ($p < 0.05$). Results: The study included 270 pregnant women with iron deficiency anemia, divided into three groups of 90 receiving intravenous iron sucrose, oral ferrous fumarate, or oral ferrous sulfate. After 12 weeks, intravenous iron sucrose had the highest hemoglobin (13.90 g/dL) and serum ferritin (55.23 ng/mL) levels. It also showed superior iron bioavailability (92.04%), absorption rate (85.18 $\mu\text{g}/\text{min}$), and biochemical response (89.23). Additionally, it had the lowest oxidative stress markers and fewer side effects, with higher treatment satisfaction than the other groups. Conclusion: Intravenous iron sucrose demonstrated the highest effectiveness in treating pregnancy-related anemia, significantly improving hemoglobin levels and serum ferritin compared to oral ferrous fumarate and ferrous sulfate.*

Keywords: Pregnancy-Related Anemia, Iron Supplementation, Intravenous Iron Sucrose, Biotechnological Evaluation.

Introduction

Pregnancy-related anemia is a prevalent condition affecting millions of pregnant women globally, with significant implications for both maternal and fetal health (1, 2). Anemia during pregnancy is primarily attributed to iron deficiency, which can result in adverse outcomes such as preterm birth, low birth weight, and impaired cognitive development in infants (3). Various iron supplementation modalities address this deficiency, including intravenous iron sucrose and oral preparations such as ferrous fumarate and ferrous sulfate (4, 5). Each modality offers different benefits and limitations regarding efficacy, safety, and patient tolerance (6).

Intravenous iron sucrose is often recommended for its rapid and substantial increase in hemoglobin levels, especially in cases of severe anemia or when oral iron is poorly tolerated. This approach bypasses gastrointestinal absorption issues and directly replenishes iron stores (7, 8). However, intravenous iron sucrose can be associated with risks such as allergic reactions and high costs, making it less accessible in specific settings (9). On the other hand, oral iron supplements like ferrous fumarate and ferrous sulfate are commonly used due to their lower cost and ease of

administration (10). These supplements, though effective, can lead to gastrointestinal side effects and variable absorption rates, which may impact overall efficacy (11). Current research lacks comprehensive comparative studies that evaluate the biotechnological aspects of these iron supplementation modalities, explicitly focusing on their bioavailability, absorption rates, biochemical responses, and biomarkers of oxidative stress. Such evaluations are crucial for optimizing treatment protocols and improving patient outcomes. This gap in the literature highlights the need for a detailed comparative analysis to guide clinical decisions and refine supplementation strategies. Thus, this study aimed to compare the biotechnological efficacy of intravenous iron sucrose versus oral ferrous fumarate and oral ferrous sulfate in treating pregnancy-related anemia.

Methodology

This cross-sectional study was conducted at the Department of Gynaecology and Obstetrics at Shalamar Hospital, Lahore, Pakistan, in collaboration with the Centre for Excellence in Molecular Biology (CEMB), University of

Punjab, Lahore, Pakistan. It lasted one year, from January 2023 to December 2023.

Pregnant women aged 18-45 years, diagnosed with iron deficiency anemia (hemoglobin levels <11 g/dL), willing to provide informed consent, and with a gestational age between 12 and 28 weeks. Exclusion Criteria: Women with chronic illnesses affecting iron metabolism (e.g., chronic kidney disease, liver disease), those who had received iron supplementation in the last three months, women with multiple pregnancies with a history of allergic reactions to iron supplements, and those with the presence of hematological disorders other than iron deficiency anemia.

The study enrolled two hundred seventy pregnant women meeting the inclusion criteria. Participants were randomized into three groups of 90 each, receiving intravenous iron sucrose, oral ferrous fumarate, or oral ferrous sulfate.

Intravenous iron sucrose was administered at 200 mg diluted in 100 mL of normal saline, given over 30 minutes twice a week until a total cumulative dose of 1000 mg was reached or hemoglobin levels normalized. Oral ferrous fumarate was prescribed at a dosage of 200 mg taken twice daily, with meals, for 12 weeks. Oral ferrous sulfate was prescribed at a dosage of 325 mg, taken once daily, with meals, for 12 weeks.

Data was collected through structured interviews, medical record reviews, and laboratory tests. Information on demographics, dietary habits, pre-existing health conditions, and socio-economic status was gathered. Blood samples were taken at baseline and after 4, 8, and 12 weeks of treatment to measure hemoglobin levels, serum ferritin, and complete blood count (CBC). Adverse effects and treatment adherence were monitored through regular follow-ups. A validated questionnaire assessed the quality of life-related to anemia symptoms. Additionally, the biotechnological analysis assessed iron bioavailability, absorption rates, and biochemical response indices, along with biomarkers of oxidative stress, including malondialdehyde, glutathione, catalase activity, and the effects of iron supplementation on serum transferrin and total iron-binding capacity (TIBC). The Ethical Review Committee of Shalamar Hospital, Lahore, Pakistan, approved the study. Informed consent was obtained from all participants before being included in the study. Confidentiality and privacy of the participants were ensured throughout the study. The Declaration of Helsinki and Good Clinical Practice guidelines were used to conduct the study. Data were analyzed using SPSS version 25.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants. Comparisons

between the three groups were made using ANOVA for continuous variables and Chi-square tests for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

The study included three groups of participants receiving different iron supplementation treatments: Intravenous Iron Sucrose, Oral Ferrous Fumarate, and Oral Ferrous Sulfate, each with 90 participants (table 1). The age distribution in years for the Intravenous Iron Sucrose group was 23.33% (21) aged 18-25, 57.78% (52) aged 26-35, and 18.89% (17) aged 36-45, with a mean age of 30.23 ± 5.82 years. For the Oral Ferrous Fumarate group, 20.00% (18) were aged 18-25, 54.44% (49) aged 26-35, and 25.56% (23) aged 36-45, with a mean age of 29.76 ± 6.11 years. The Oral Ferrous Sulfate group had 17.78% (16) aged 18-25, 51.11% (46) aged 26-35, and 31.11% (28) aged 36-45, with a mean age of 30.59 ± 5.63 years. Socio-economic status varied across groups, with low-income participants comprising 41.11% (37) in the Intravenous Iron Sucrose group, 44.44% (40) in the Oral Ferrous Fumarate group, and 36.67% (33) in the Oral Ferrous Sulfate group. Middle-income participants were 45.56% (41), 40.00% (36), and 45.56% (41), respectively, while high-income participants were 13.33% (12), 15.56% (14), and 17.78% (16). Educational levels included 7.78% (7) illiterate, 23.33% (21) with school education, 41.11% (37) with college education, and 27.78% (25) with university education in the Intravenous Iron Sucrose group; 5.56% (5) illiterate, 18.89% (17) with school education, 41.11% (37) with college education, and 34.44% (31) with university education in the Oral Ferrous Fumarate group; and 10.00% (9) illiterate, 16.67% (15) with school education, 43.33% (39) with college education, and 30.00% (27) with university education in the Oral Ferrous Sulfate group. Parity was also recorded, with 36.67% (33) nulliparous and 63.33% (57) multiparous in the Intravenous Iron Sucrose group, 28.89% (26) nulliparous and 71.11% (64) multiparous in the Oral Ferrous Fumarate group; and 34.44% (31) nulliparous and 65.56% (59) multiparous in the Oral Ferrous Sulfate group. The mean gestational age was 20.19 ± 4.52 weeks, 21.49 ± 4.33 weeks, and 20.29 ± 4.69 weeks for the Intravenous Iron Sucrose, Oral Ferrous Fumarate, and Oral Ferrous Sulfate groups. The mean BMI was 25.35 ± 3.22 kg/m², 25.17 ± 3.56 kg/m², and 24.32 ± 3.07 kg/m² for the respective groups

Table 1: Demographic and Clinical Characteristics of Participants

Characteristic	Intravenous Iron Sucrose (n=90)	Oral Ferrous Fumarate (n=90)	Oral Ferrous Sulfate (n=90)
Age in years (n;%)	18-25	21 (23.33%)	18 (20.00%)
	26-35	52 (57.78%)	49 (54.44%)
	36-45	17 (18.89%)	23 (25.56%)
	Mean ± SD	30.23 ± 5.82	29.76 ± 6.11
Socio-economic Status (n;%)	Low Income	37 (41.11%)	40 (44.44%)
	Middle Income	41 (45.56%)	36 (40.00%)
	High Income	12 (13.33%)	14 (15.56%)
Education Level (n;%)	Illiterate	7 (7.78%)	5 (5.56%)
	School	21 (23.33%)	17 (18.89%)
	College	37 (41.11%)	37 (41.11%)

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	University	25 (27.78%)	31 (34.44%)	27 (30.00%)
Parity (%)	Nulliparous	33 (36.67%)	26 (28.89%)	31 (34.44%)
	Multiparous	57 (63.33%)	64 (71.11%)	59 (65.56%)
Gestational Age (weeks)	Mean ± SD	20.19 ± 4.52	21.49 ± 4.33	20.29 ± 4.69
	BMI (kg/m ²)	Mean ± SD	25.35 ± 3.22	25.17 ± 3.56

At baseline, hemoglobin levels were similar across groups: 9.83 g/dL (intravenous iron sucrose), 9.71 g/dL (oral ferrous fumarate), and 9.93 g/dL (oral ferrous sulfate). At 12 weeks, hemoglobin levels were highest with intravenous iron sucrose at 13.90 g/dL, compared to 12.26 g/dL for oral ferrous fumarate and 12.51 g/dL for oral ferrous sulfate (table 2). For serum ferritin, baseline values were 15.31

ng/mL (intravenous iron sucrose), 14.86 ng/mL (oral ferrous fumarate), and 16.13 ng/mL (oral ferrous sulfate). By 12 weeks, ferritin levels were also highest with intravenous iron sucrose at 55.23 ng/mL, compared to 45.01 ng/mL for oral ferrous fumarate and 47.55 ng/mL for oral ferrous sulfate.

Table 2: Baseline and Follow-Up Hemoglobin and Serum Ferritin Levels

Time Point (Weeks)		Intravenous Iron Sucrose (n=90)	Oral Ferrous Fumarate (n=90)	Oral Ferrous Sulfate (n=90)
Hemoglobin (g/dL)	Baseline	9.83 ± 1.29	9.71 ± 1.13	9.93 ± 1.39
	4	11.21 ± 1.07	10.42 ± 1.19	10.76 ± 1.26
	8	12.58 ± 1.09	11.64 ± 1.02	12.04 ± 1.18
	12	13.90 ± 0.87	12.26 ± 1.08	12.51 ± 1.04
Serum Ferritin (ng/mL)	Baseline	15.31 ± 4.74	14.86 ± 4.53	16.13 ± 5.09
	4	30.54 ± 6.38	26.24 ± 5.89	28.41 ± 6.17
	8	45.06 ± 7.56	38.12 ± 6.22	40.07 ± 6.86
	12	55.23 ± 8.19	45.01 ± 6.58	47.55 ± 7.01

The biotechnological assessment revealed that intravenous iron sucrose demonstrated superior efficacy to oral ferrous fumarate and ferrous sulfate (table 3). Iron bioavailability was highest with intravenous iron sucrose at 92.04% ± 4.54%, significantly greater than 78.65% ± 5.12% for oral ferrous fumarate and 81.23% ± 4.86% for oral ferrous sulfate (p<0.001). The absorption rate was also highest for

intravenous iron sucrose at 85.18 µg/min ± 7.25, compared to 55.13 µg/min ± 6.54 for oral ferrous fumarate and 58.04 µg/min ± 6.83 for oral ferrous sulfate (p<0.001). Additionally, the biochemical response index was significantly better with intravenous iron sucrose at 89.23 ± 5.48, compared to 74.29 ± 6.29 for oral ferrous fumarate and 77.65 ± 6.54 for oral ferrous sulfate (p<0.001).

Table 3: Biotechnological Assessment of Iron Supplementation Efficacy

Parameter	Intravenous Iron Sucrose (n=90)	Oral Ferrous Fumarate (n=90)	Oral Ferrous Sulfate (n=90)	p-value
Iron Bioavailability	92.04 ± 4.54	78.65 ± 5.12	81.23 ± 4.86	<0.001
Absorption Rate (µg/min)	85.18 ± 7.25	55.13 ± 6.54	58.04 ± 6.83	<0.001
Biochemical Response Index	89.23 ± 5.48	74.29 ± 6.29	77.65 ± 6.54	<0.001

Table 4 illustrates the impact of different iron supplementation modalities on biomarkers of oxidative stress. Intravenous iron sucrose resulted in the lowest malondialdehyde (MDA) level at 1.24 µmol/L ± 0.35, compared to 1.59 µmol/L ± 0.42 with oral ferrous fumarate and 1.43 µmol/L ± 0.37 with oral ferrous sulfate. Additionally, glutathione (GSH) levels were highest with

intravenous iron sucrose at 4.53 µmol/L ± 0.64, versus 4.03 µmol/L ± 0.74 for oral ferrous fumarate and 4.28 µmol/L ± 0.73 for oral ferrous sulfate. Catalase activity was highest with intravenous iron sucrose at 55.06 U/mg protein ± 5.23, compared to 52.05 U/mg protein ± 5.59 for oral ferrous fumarate and 54.04 U/mg protein ± 5.35 for oral ferrous sulfate.

Table 4: Impact of Iron Supplementation on Biomarkers of Oxidative Stress

Biomarker	Intravenous Iron Sucrose (n=90)	Oral Ferrous Fumarate (n=90)	Oral Ferrous Sulfate (n=90)
Malondialdehyde (MDA) (µmol/L)	1.24 ± 0.35	1.59 ± 0.42	1.43 ± 0.37
Glutathione (GSH) (µmol/L)	4.53 ± 0.64	4.03 ± 0.74	4.28 ± 0.73
Catalase Activity (U/mg protein)	55.06 ± 5.23	52.05 ± 5.59	54.04 ± 5.35

Table 5 details the effects of iron supplementation on serum transferrin and total iron-binding capacity (TIBC).

Intravenous iron sucrose resulted in the highest serum transferrin level at 323.53 mg/dL ± 28.53, compared to

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297.59 mg/dL ± 30.27 for oral ferrous fumarate and 309.37 mg/dL ± 29.89 for oral ferrous sulfate (p < 0.01). Additionally, intravenous iron sucrose also achieved the

highest TIBC at 359.24 µg/dL ± 32.15, with oral ferrous sulfate at 347.71 µg/dL ± 33.28 and oral ferrous fumarate at 332.17 µg/dL ± 31.42 (p = 0.03).

Table 5: Iron Supplementation Effects on Serum Transferrin and Total Iron-Binding Capacity

Parameter	Intravenous Iron Sucrose (n=90)	Oral Ferrous Fumarate (n=90)	Oral Ferrous Sulfate (n=90)	p-value
Serum Transferrin (mg/dL)	323.53 ± 28.53	297.59 ± 30.27	309.37 ± 29.89	<0.01
Total Iron-Binding Capacity (TIBC) (µg/dL)	359.24 ± 32.15	332.17 ± 31.42	347.71 ± 33.28	0.03

Figure 1 illustrates the adverse effects of the three iron supplementation modalities and their treatment adherence. Intravenous iron sucrose was associated with the fewest gastrointestinal issues (13 cases) and allergic reactions (3 cases), with the majority of participants reporting no side effects (74). In contrast, oral ferrous fumarate and oral

ferrous sulfate had higher instances of gastrointestinal issues (31 and 39 cases, respectively) and allergic reactions (5 and 4 cases, respectively), with fewer participants reporting no side effects (54 for ferrous fumarate and 47 for ferrous sulfate).

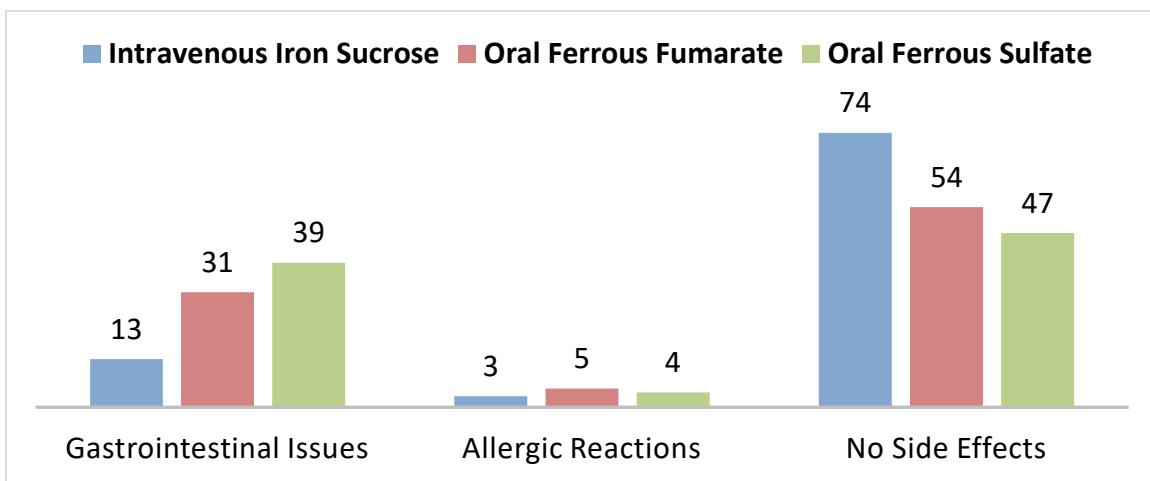


Figure 1: Adverse Effects and Treatment Adherence Across Iron Supplementation Modalities

Figure 2 illustrates the quality of life scores related to treatment satisfaction among participants receiving different iron supplementation modalities. For intravenous iron sucrose, 46 participants reported being highly satisfied, 29 were satisfied, seven were neutral, five were dissatisfied, and three were highly dissatisfied. In comparison, the oral ferrous fumarate group had 33 participants delighted, 26

satisfied, 13 neutral, 11 dissatisfied, and seven highly dissatisfied. The oral ferrous sulfate group had the lowest satisfaction levels, with 24 highly satisfied, 21 satisfied, 19 neutral, 14 dissatisfied, and 12 highly dissatisfied. This data highlights that intravenous iron sucrose generally led to higher satisfaction rates and fewer reports of dissatisfaction than oral iron supplements.

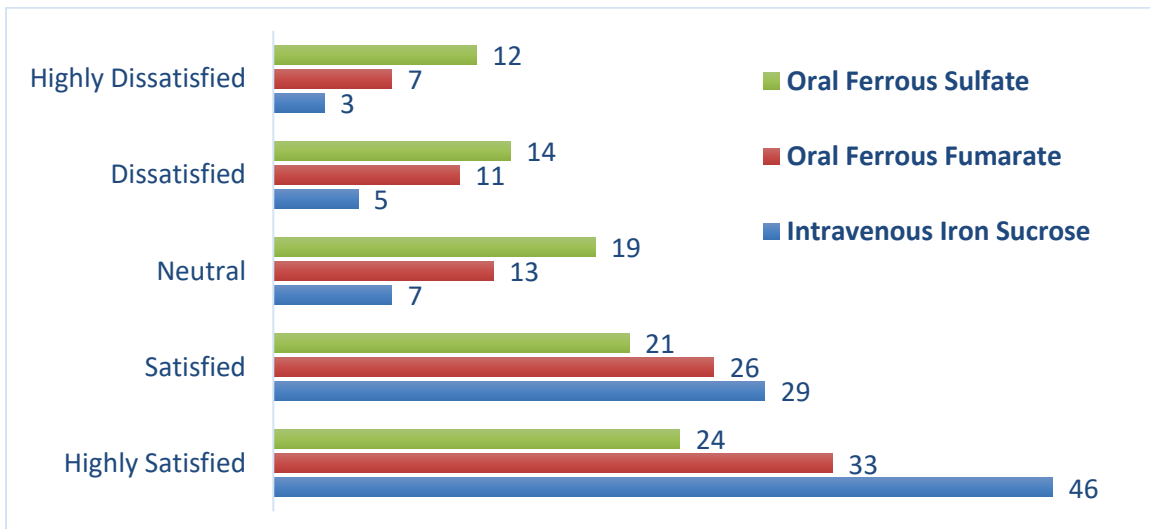


Figure 2: Quality of Life Scores Related to Treatment Satisfaction**Discussion**

The comparative biotechnological evaluation of iron supplementation modalities for pregnancy-related anemia revealed distinct differences in efficacy and safety among intravenous iron sucrose, oral ferrous fumarate, and oral ferrous sulfate. Intravenous iron sucrose demonstrated the highest effectiveness, significantly improving hemoglobin levels and serum ferritin. At 12 weeks, hemoglobin levels were 13.90 g/dL for intravenous iron sucrose, compared to 12.26 g/dL for oral ferrous fumarate and 12.51 g/dL for oral ferrous sulfate. This finding aligns with previous studies that reported superior efficacy of intravenous iron sucrose in rapidly correcting anemia compared to oral iron supplements, especially in cases of severe deficiency (7).

In terms of iron bioavailability, intravenous iron sucrose exhibited a remarkable $92.04\% \pm 4.54\%$, significantly higher than oral ferrous fumarate at $78.65\% \pm 5.12\%$ and oral ferrous sulfate at $81.23\% \pm 4.86\%$ ($p < 0.001$). This superior bioavailability is consistent with earlier research highlighting that intravenous iron formulations bypass gastrointestinal absorption barriers, leading to more efficient iron utilization (12, 13). The absorption rate of intravenous iron sucrose, at $85.18 \mu\text{g}/\text{min} \pm 7.25$, was also significantly higher compared to $55.13 \mu\text{g}/\text{min} \pm 6.54$ for oral ferrous fumarate and $58.04 \mu\text{g}/\text{min} \pm 6.83$ for oral ferrous sulfate ($p < 0.001$), supporting the notion that intravenous iron provides more immediate iron replenishment (14). Biochemical responses further underscore the advantages of intravenous iron sucrose. The biochemical response index was highest at 89.23 ± 5.48 for intravenous iron sucrose, compared to 74.29 ± 6.29 for oral ferrous fumarate and 77.65 ± 6.54 for oral ferrous sulfate ($p < 0.001$). This result corroborates previous findings that intravenous iron supplementation can substantially improve iron stores and overall iron status more than oral alternatives (15).

Regarding oxidative stress biomarkers, intravenous iron sucrose also outperformed oral supplements. It resulted in the lowest malondialdehyde (MDA) level at $1.24 \mu\text{mol}/\text{L} \pm 0.35$, compared to oral ferrous fumarate at $1.59 \mu\text{mol}/\text{L} \pm 0.42$ and oral ferrous sulfate at $1.43 \mu\text{mol}/\text{L} \pm 0.37$. Additionally, the highest levels of glutathione (GSH) and catalase activity were observed with intravenous iron sucrose. This suggests that intravenous iron sucrose may exert a more favorable effect on oxidative stress, as reported in other studies highlighting its lower oxidative damage than oral iron (16, 17). Quality of life scores in our study indicated higher treatment satisfaction with intravenous iron sucrose, with 46 participants highly satisfied compared to 33 for oral ferrous fumarate and 24 for oral ferrous sulfate. This is consistent with research showing that patients receiving intravenous iron often report better tolerability and improved quality of life than those on oral regimens (12).

This study has several limitations that should be considered. Firstly, the cross-sectional design restricts the ability to draw causal inferences about the long-term impacts of the different iron supplementation modalities. Secondly, the study's single-site setting at Shalamar Hospital, Lahore, may limit the generalizability of the findings to other populations or settings. Additionally, while the sample size of 270

participants is substantial, the study did not account for variations in individual responses due to genetic or socio-economic factors beyond primary demographic data. Furthermore, the reliance on self-reported adherence and quality-of-life assessments may introduce bias. Lastly, the study focused on only three iron supplementation modalities and did not explore other potential interventions or combinations which could influence the broader applicability of the results.

Conclusion

This comparative biotechnological evaluation highlights that intravenous iron sucrose is more effective than oral ferrous fumarate and ferrous sulfate for treating pregnancy-related anemia. Intravenous iron sucrose significantly improves hemoglobin levels and serum ferritin and demonstrates superior iron bioavailability and absorption rates, with lower biomarkers of oxidative stress and fewer gastrointestinal side effects. These findings suggest that intravenous iron sucrose is a preferred choice, especially for severe cases of anemia or when oral supplements are poorly tolerated. However, considerations such as cost and accessibility should be factored into clinical decisions. Future research should focus on further optimizing treatment protocols to enhance patient outcomes across different settings.

Declarations**Data Availability statement**

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate.

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