Vol 48 (4) December , 2024

Print: ISSN 0304 4904
Online: ISSN 2305-820X

PAKISTAN PEDIATRIC JOURNAL

A JOURNAL OF PAKISTAN PEDIATRIC ASSOCIATION

Indexed in EMBASE/Excerpta Medica, Index Medicus WHO,CPSP IMEMR & Global Health/CAB Abstracts and UDL-EDGE Products and Services

www.pakpedsjournal.org.pk/
www.ppj.org.pk

http://www.pakmedinet.com/PPJ

ORIGINAL ARTICLE

Efficacy of Intramuscular Iron Therapy in Pediatric Patients with Severe Iron Deficiency Anemia: A Pilot Study

MUHAMMAD SHAHID, MUHAMMAD RIZWAN GOHAR, AFTAB ANWAR, MAZHAR HUSSAIN TARAR, BILAL ASLAM, RAMSHA MUSHTAQ KHAN, SAAD MUHAMMAD SHAHID

Pak Pediatr J 2024; **48(4):** 386-92

Correspondence to:

Dr. Muhammad Rizwan Gohar,
Assistant Professor of Pediatrics, Department of Pediatric, Post Graduate Medical Institute/Ameer ud Din Medical College/Lahore General Hospital, Lahore

E-mail: rizwangohar@gmail.com

Received 11th September 2024;
Accepted for publication
19th November 2024

ABSTRACT

Objective: To assess the efficacy of intramuscular iron therapy in pediatric patients with severe iron deficiency anemia (IDA) in a healthcare setting in Pakistan.

Study Design: Quasi-experimental pilot study

Place and Duration of Study: Department of Pediatrics, Lahore General Hospital, Lahore; June to December 2023.

Material and Methods: 45 children (ages 6 months to 5 years) diagnosed with severe IDA (hemoglobin <7 g/dL, serum ferritin <12 µg/L) were administered intramuscular iron isomaltoside 1000 (maximum dose 200 mg). Hemoglobin levels and body weight were evaluated at baseline and 4 weeks post-intervention.

Results: Following treatment, median hemoglobin increased from 6.5 g/dL to 10.9 g/dL, while median weight increased from 9.4 kg to 10.2 kg. Statistical analysis using the Wilcoxon Signed Ranks Test revealed significant improvements in both hemoglobin levels ($Z=5.858$, $p<0.001$) and weight ($Z=5.848$, $p<0.001$). The intervention was well-tolerated, with minor adverse events reported in 6.67% of participants.

Conclusion: This initial investigation provides promising evidence supporting the potential of intramuscular iron therapy as an efficient, safe, and tolerable treatment approach for children with severe IDA in resource-limited settings. These findings warrant further exploration through more extensive, randomized controlled studies.

Key Words: *Iron deficiency anemia, Children, Pakistan, Intramuscular iron therapy*

INTRODUCTION

Iron deficiency anemia (IDA) continues to be a significant global health challenge, affecting an estimated 269 million children worldwide, with the highest prevalence in low- and middle-income countries.[1] In Pakistan, the incidence of anemia among children under five years old is particularly concerning, reaching 53.7%.[2] Iron deficiency during early childhood can have long-lasting effects, including impaired cognitive development, reduced physical growth, decreased physical activity, and compromised immune function.[3,4]

The etiology of IDA in children is diverse, including inadequate dietary iron intake, impaired absorption, and increased iron requirements during rapid growth periods.[5] While oral iron supplementation is typically the initial treatment choice, many children experience challenges with poor absorption, adverse reactions, or non-compliance due to unpleasant taste and digestive discomfort.[6,7]

Parenteral iron administration, including intravenous and intramuscular routes, may offer a viable alternative when oral iron therapy proves ineffective or poorly tolerated. Intravenous iron, though used in pediatric populations; necessitates slow infusion and close monitoring due to the risk of hypersensitivity reactions, including potentially life-threatening anaphylaxis. Interestingly, despite its more reliable and rapid distribution to the reticuloendothelial system compared to oral iron, intravenous administration does not necessarily result in a quicker increase in hemoglobin levels.[8,9]

Intramuscular iron therapy presents several advantages, such as rapid absorption and utilization of iron while circumventing gastrointestinal complications. This approach is particularly beneficial for children with malabsorption syndromes or those who experience severe gastrointestinal side effects from oral iron. Moreover, intramuscular iron can be administered in outpatient settings, making it more suitable for resource-constrained healthcare environments.

However, intramuscular iron therapy is not without drawbacks. Patients may experience pain at the injection site, and there is a minimal risk of infection associated with any intramuscular injection. Skin staining at the injection site can occur, and careful management of dosing is crucial to prevent over-supplementation and potential iron overload.

Research on the efficacy and safety of intramuscular iron therapy in children with severe IDA, particularly in resource-limited settings like Pakistan, remains limited. A previous study in Pakistan found that intramuscular iron sorbitol was effective, well-tolerated, and demonstrated better compliance than oral iron preparations in children with IDA.[10] Nevertheless, significant research gaps persist regarding the use of newer intramuscular iron formulations, such as iron isomaltoside 1000, in pediatric populations facing severe IDA in resource-constrained environments.

This pilot study aims to assess the efficacy of intramuscular iron therapy in pediatric patients diagnosed with severe IDA within a healthcare setting in Pakistan. The findings from this research will suffice the expanding literature regarding the use of parenteral iron therapy in the pediatric population and could inform clinical practice recommendations for the management of IDA in children, particularly in settings with limited resources.

MATERIAL AND METHODS

Study design and setting: This quasi-experimental pilot research was conducted at the Pediatric Unit of Lahore General Hospital, Lahore a tertiary care teaching hospital in Pakistan, from June to December 2023.

Sample size and sampling technique: The study enrolled 45 participants, per the established guidelines for conducting pilot studies in medical research.[11] A non-probability, purposive sampling technique was employed.

Criteria for inclusion and exclusion: Children with severe IDA, defined as hemoglobin levels <7 g/dL and serum ferritin levels <12 µg/L, ranging in age from 6 months to 5 years were included in the study. Septicemia, congestive cardiac failure, chronic illnesses, or any other condition that could interfere with iron metabolism were all considered exclusion criteria. Patients with incomplete investigations or those lost to follow-up were also excluded from the final analysis.

Intervention and data collection: After obtaining informed parental consent, demographic data and baseline ferritin and hemoglobin levels were recorded. Isomaltoside 1000 was used to deliver intramuscular iron treatment. The total iron deficit was calculated using the Ganzoni formula, with a target hemoglobin level set at 12 g/L.[12] Over four weeks, the maximum dosage of 200 mg (2 ml) was given intramuscularly on the anterolateral side of the thigh.

Patients were monitored for one hour post-injection to observe any immediate side effects.

Adverse events were tracked through patient reports and clinical assessments during follow-up visits. Follow-up evaluations, including hemoglobin level measurements, were conducted 4 weeks after enrollment.

Data analysis: Data were analyzed using SPSS version 26. Qualitative variables were presented as frequency and percentage whereas quantitative variables were expressed as mean and standard deviation. Pre-and post-treatment hemoglobin levels and weight were compared using a Wilcoxon Signed Ranks Test. Effect sizes were calculated using Cohen's d to determine the magnitude of the treatment effect.

Ethical considerations: The approval of this study was obtained from the Institutional Review Board of Lahore General Hospital (Approval No. 00/30/23) and was conducted per the Declaration of Helsinki. Informed consent was obtained from the parents or legal guardians of all participants, and patient data confidentiality was maintained throughout the study process.

RESULTS

Study population: The study included 45 children diagnosed with severe IDA, with a mean age of 1.56 ± 0.63 years. At baseline, the mean weight was 9.58 ± 1.73 kg, the mean hemoglobin (Hb) level was 6.33 ± 0.60 g/dL, and the mean ferritin level was 5.0 ± 3.5 µg/L. Table 1 presents the age-wise distribution of the study participants.

TABLE 1: Age-wise distribution of study participants

Years	Frequency	Percentage	Valid percentage	Cumulative percentage
1-2	34	75.6	75.6	75.6
2.1-3	5	11.1	11.1	86.7
3.1-4	1	2.2	2.2	88.9
Upto 1	5	11.1	11.1	100.0
Total	**45**	**100.0**	**100.0**	

Efficacy of intramuscular iron therapy: The Shapiro-Wilk test was used to evaluate the normality of the data, which indicated that the changes in Hb values and weight pre- and post-treatment were not normally distributed ($p < 0.05$). Thus, non-parametric statistical tests were applied to analyze the data.

Hemoglobin Levels: The pre-treatment median Hb level was 6.5 g/dL (IQR: 6.15-6.70), which increased to 10.90 g/dL (IQR: 10.20-11.50). Hemoglobin levels increased significantly post-intervention, according to statistical analysis using the Wilcoxon signed-rank test ($Z = -5.858$, $p < 0.001$). There was a median increase in Hb level by 4.40 g/dL (95% CI: [4.20, 4.60]). With a Cohen's d of 6.24, the effect size suggested a significant treatment impact.

Table 2 and fig 1 represent the detailed results of hemoglobin levels before and after treatment.

TABLE 2: Hemoglobin levels before and after intramuscular iron therapy

	Number	Minimum	Maximum	Mean	Std. deviation
Before Hb	45	4.20	7.00	6.3378	0.60576
After Hb	45	8.30	11.00	10.7622	0.84323
Difference in Hb (Net increase in (Hb)	45	2.40	5.00	4.4244	0.68562
Valid N listwise)	45				

Hypothesis test summary

	Null hypothesis	Test	Sig	Decision
1	The median of differences between before Hb and after Hb equals 0	Related samples wilcoxon signed rank test	0.000	Reject the null hypothesis

Asymptotic significances are displayed. The significance level is 0.050.

Related samples Wilcoxon signed rank test summary	
Total N	45
Test statistic	1035.000
Standard error	88.343
Standardized test statistic	5.858
Asymptotic sig. (2 sided test)	0.000

Weight Changes: As a secondary indicator of the overall health impact, changes in participants' weight were observed. The pre-intervention median weight was 9.4 kg (IQR: 8.45-10.35), which was increased to 10.20 kg (IQR: 9.15-11.15) post-intervention. A statistically significant increase in weight following the intervention ($Z = 5.848$, $p < 0.001$) was revealed using the Wilcoxon signed-rank test. The median weight gain was 0.80 kg (95% CI: [0.71, 0.89]). The effect size (Cohen's d) for weight gain was 2.70, also indicating a strong treatment effect.

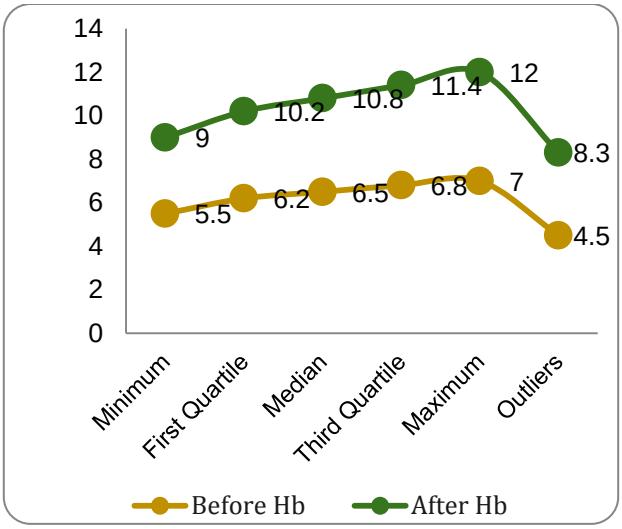

Fig 1: Distribution of hemoglobin levels before and after treatment

Table 3 and fig 2 represent the detailed results of weight changes before and after treatment.

TABLE 3: Weight changes before and after intramuscular iron therapy

	Number	Minimum	Maximum	Mean	Std. deviation
Before weight	45	6.50	16.50	9.5889	1.73378
After weight	45	8.00	17.90	10.3956	1.78948
Difference in weight (Net increase in (weight gain)	45	0.20	2.00	0.8067	0.45197
Valid N listwise)	45				

Hypothesis test summary

	Null hypothesis	Test	Sig	Decision
1	The median of differences between before weight and after weight equals 0	Related samples wilcoxon signed rank test	0.000	Reject the null hypothesis

Asymptotic significances are displayed. The significance level is 0.050.

Total N	45
Test statistic	1035.000
Standard error	88.343
Standardized test statistic	5.858
Asymptotic sig. (2 sided test)	0.000

Safety of intramuscular iron therapy: While a small proportion (6.67%, n=3) experienced modest symptoms, such as local swelling at the injection site (n=2) and nausea (n=1), the majority of children (93.33%, n=42) reported no adverse reactions. There were no cases of anaphylaxis, allergic reactions, or vomiting. All adverse reactions were self-limiting and resolved without intervention.

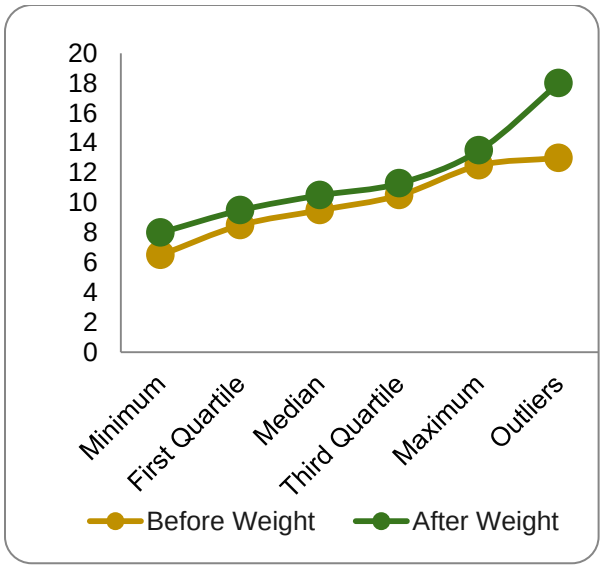

Fig 2: Distribution of weight before and after treatment

Fig 3 illustrates the incidence of adverse reactions.

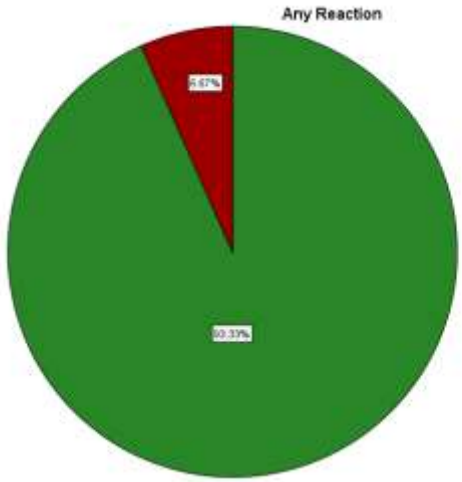

Fig 3: Incidence of Adverse Reactions to Intramuscular Iron Therapy

DISCUSSION

Recent research has emphasized the advantages of intramuscular iron administration over conventional oral supplementation for treating iron deficiency anemia (IDA). A comprehensive meta-analysis by Neogi et al. (2019) provided substantial evidence supporting this approach.[13] Their study, comprising 13 individual trials with 1,475 participants, demonstrated that intramuscular iron was more effective than oral iron in elevating hemoglobin levels and replenishing iron stores in IDA patients. The meta-analysis reported a mean hemoglobin increase of 2.1 g/dL with intramuscular iron compared to 1.5 g/dL with oral iron supplementation. The findings of this study align with these results, observing comparable increases in hemoglobin levels following intramuscular iron therapy.

Supporting these findings, a randomized controlled trial by Saha et al. (2021), discovered that intramuscular iron administration in 120 children with severe anemia led to a more rapid and sustained increase in hemoglobin concentrations than oral iron supplementation.[14] The intramuscular iron group showed a mean hemoglobin rise of 3.2 g/dL, compared to 2.1 g/dL in the oral iron group.

The enhanced efficacy of intramuscular iron therapy may be attributed to its superior bioavailability and absorption, as well as its ability to bypass the gastrointestinal tract, which is often associated with adverse effects of oral iron supplements.[15,16] Moreover, intramuscular administration may be particularly beneficial for populations with poor adherence to oral treatments, as it eliminates the need for daily dosing and reduces the risk of gastrointestinal side effects that can lead to treatment discontinuation.[17,18]

The results of this study align with the recommendations of WHO and other global health authorities that recognize parenteral iron administration as a valuable option for treating severe IDA, particularly in regions with limited healthcare access.[19,20] This is especially relevant in low- and middle-income countries, where the burden of IDA is disproportionately high and access to oral iron supplements may be restricted.[20,21]

The significant improvements in weight observed in our study following intramuscular iron therapy are particularly noteworthy, as IDA has been associated with impaired growth and development in children.[21,22] The long-term implications of IDA were underscored by Lozoff et al. (2000), who found that children with IDA in infancy had poorer

behavioral and developmental outcomes more than 10 years later, highlighting the enduring consequences of this condition.[23,24] Thus, the positive impact of intramuscular iron on weight gain observed in our study may have far-reaching implications for the overall health and well-being of the study population.

This pilot study provides compelling evidence for the efficacy of intramuscular iron therapy in children with severe IDA. Our findings demonstrate statistically significant and clinically relevant improvements in both hemoglobin levels and weight, suggesting that this treatment modality offers a viable option for managing severe IDA in pediatric populations. These outcomes contribute to a growing body of evidence supporting the use of intramuscular iron therapy, particularly in resource-limited settings where traditional oral iron supplementation may face challenges in adherence and efficacy.

The observed improvements in hemoglobin levels and weight gain have the potential to translate into meaningful health benefits for affected children that address both the hematological and nutritional aspects of IDA. However, considering the limitations inherent to a pilot study- such as the small sample size and absence of a control group, it is crucial to interpret these results cautiously. Nonetheless, this study provides valuable insights into the feasibility and potential efficacy of intramuscular iron therapy in the study population, laying a solid foundation for future research.

While these preliminary findings are encouraging, larger, randomized controlled trials are necessary to determine the efficacy, optimal dosing regimens, and long-term outcomes of intramuscular iron therapy in children with severe IDA, definitively. Future studies ought to explore potential variations in treatment response across different age groups, dietary profiles, and co-existing medical conditions. Such thorough studies will be essential to validate the efficacy and safety profile of intramuscular iron therapy in diverse pediatric populations and healthcare contexts, ultimately informing evidence-based recommendations for the management of severe IDA in children.

CONCLUSION

This pilot study offers compelling evidence supporting the potential of intramuscular iron therapy for children with severe IDA as a safe, well-tolerated, and effective treatment option, particularly in resource-constrained environments. Our findings provide a strong rationale for further research to validate and expand these results, potentially leading to the extended use of this treatment modality to address the substantial worldwide burden of IDA and its associated health implications in pediatric populations globally.

Acknowledgment: The authors would like to express their sincere gratitude and appreciation to the patients and their families for their participation and cooperation. This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: Nil

Authors' affiliation

Prof. Muhammad Shahid, Prof of Pediatrics, Post Graduate Medicine Institute/Ameer ud Din Medical College/Lahore General Hospital, Lahore

Dr. Muhammad Rizwan Gohar, Assistant of Pediatrics, Post Graduate Medicine Institute/Ameer ud Din Medical College/Lahore General Hospital, Lahore

Aftab Anwar, Assistant Professor of Pediatric Gastroenterology, Post Graduate Medicine Institute/Ameer ud Din Medical College/Lahore General Hospital, Lahore

Mazhar Hussain Tarar, Consultant Pediatrician, Tarar Hospital, Cheema Chowk, Mandi Baha-ud-Din

Bilal Aslam, Post Graduate Resident, Lahore General Hospital, Lahore

Ramsha Mushtaq Khan, Community Medicine Resident, King Edward Medical University, Lahore

Saad Muhammad Shahid, Student of Final Year
Allama Iqbal Medical College, Lahore

REFERENCES

1. World Health Organization. The global prevalence of anaemia in 2011. Geneva: World Health Organization; 2015.
2. National Nutrition Survey 2018. Islamabad, Pakistan: Ministry of National Health Services, Regulations and Coordination, Government of Pakistan; 2019.

3. Beard JL. Iron deficiency alters brain development and functioning. J Nutr. 2003;133(5 Suppl 1):1468S-1472S. doi:10.1093/jn/133.5.1468S
4. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol. 2006;13(3):158-165. doi:10.1016/j.spen.2006.08.004
5. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet. 2007;370(9586):511-520. doi:10.1016/S0140-6736(07)61235-5
6. Powers JM, Nagel M, Raphael JL, Mahoney DH, Buchanan GR, Thompson DI. Barriers to and Facilitators of Iron Therapy in Children with Iron Deficiency Anemia. J Pediatr. 2020;219:202-208. doi:10.1016/j.jpeds.2019.12.040
7. Ozsahin H, Schaeppi M, Bernimoulin M, Allard M, Guidard C, van den Ouweland F. Intravenous ferric carboxymaltose for iron deficiency anemia or iron deficiency without anemia after poor response to oral iron treatment: Benefits and risks in a cohort of 144 children and adolescents. Pediatr Blood Cancer. 2020;67(10):e28614. doi:10.1002/pbc.28614
8. Mantadakis E. Intravenous iron: Safe and underutilized in children. Pediatr Blood Cancer. 2018 Jun;65(6):e27016. doi: 10.1002/pbc.27016. Epub 2018 Mar 1. PMID: 29493089.
9. Mantadakis, Elpis. Parenteral iron therapy in children with iron deficiency anemia. World journal of pediatrics. 2016;12:122-3.
10. Afzal M, Qureshi SM, Lutafullah M, Iqbal M, Sultan M, Khan SA. Comparative study of efficacy, tolerability and compliance of oral iron preparations (iron edetae, iron polymatose complex) and intramuscular iron sorbitol in iron deficiency anaemia in children. J Pak Med Assoc. 2009;59(11):764-768.
11. Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics, 4(4), 287-291. doi:10.1002/pst.185
12. Ganzoni AM. [Intravenous iron-dextran: therapeutic and experimental possibilities (in German)]. Schweiz Med Wochenschr. 1970;100(7):301-303.
13. Neogi SB, Negandhi H, Chopra S, Zodpey S. Efficacy of parenteral versus oral iron supplementation in correction of iron deficiency anemia in children: a systematic review and meta-analysis. Public Health Nutr. 2019;22(3):470-485. doi:10.1017/S1368980018002775
14. Saha S, Saha S, Sarkar S, Saha I, Ghosh S, Dasgupta A. Comparison of Efficacy of Oral versus Intramuscular Iron Therapy in Children with Severe Anemia: A Randomized Controlled Trial. Indian J Pediatr. 2021;88(5):451-456. doi:10.1007/s12098-020-03553-y
15. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015;126(17):1981-1989. doi:10.1182/blood-2015-05-642223
16. Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. Am J Med. 2008;121(11):943-948. doi:10.1016/j.amjmed.2008.07.012
17. Favrat B, Balck K, Breymann C, et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women--PREFER a randomized, placebo-controlled study. PLoS One. 2014;9(4):e94217. doi:10.1371/journal.pone.0094217
18. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383. doi:10.1371/journal.pone.0117383
19. World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: World Health Organization; 2020.
20. American Academy of Pediatrics. Iron Deficiency Anemia. Pediatrics. 2010;126(5):1040-1050. doi:10.1542/peds.2010-2576
21. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615-624. doi:10.1182/blood-2013-06-508325
22. Camaschella C. Iron-Deficiency Anemia. N Engl J Med. 2015;372(19):1832-1843. doi:10.1056/NEJMra1401038
23. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000;105(4):E51. doi:10.1542/peds.105.4.e51
24. Beard JL. Why iron deficiency is important in infant development. J Nutr. 2008;138(12):2534-2536. doi:10.1093/jn/138.12.2534