Advancements in Anemia Management during Pregnancy: The Role of Recombinant Erythropoietin and Dietary Interventions

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Abstract: **Anemia during pregnancy, predominantly caused by iron deficiency, remains a major global health concern, particularly in low- and middle-income countries. This review compiles evidence from 25 significant studies assessing various biotechnological and dietary approaches to manage and mitigate iron-deficiency anemia (IDA) in pregnant women. Interventions such as recombinant erythropoietin, iron-fortified foods, micronutrient-rich beverages, and iron-folic acid supplementation have demonstrated variable success in improving maternal hemoglobin and iron status. While daily iron supplementation proves more effective than intermittent strategies, concerns about side effects and compliance persist. Nutritional counseling and fortified diets, especially when combined with targeted supplementation strategies, significantly reduce anemia prevalence and improve maternal and neonatal outcomes. Moreover, studies highlight the importance of micronutrients like zinc, vitamin C, and vitamin D in supporting hematopoiesis and enhancing iron absorption. Innovations in delivery methods, such as prolonged-release supplements and direct observation for improved adherence, also show promise. However, gaps in early pregnancy supplementation, disparities in resource access, and variations in compliance continue to hinder large-scale effectiveness. This review underscores the need for integrative, personalized, and evidence-based anemia management strategies that combine biotechnology.**

Keywords: **Iron Deficiency, Recombinant Erythropoietin, Iron Supplementation, Dietary Intervention, Fortified Foods, Maternal Health**

INTRODUCTION

Skolmowska D. et. al. (2022) conducted a systematic review to assess the effectiveness of dietary interventions, such as iron-rich or fortified foods, multi-nutrient intake, and dietary counselling—in preventing and treating iron-deficiency anemia in pregnant women. The findings showed that these interventions were generally effective, but many of the included studies had a medium to high risk of bias, indicating a need for more rigorous randomized controlled trials in the future [1]. During pregnancy, iron requirements increase significantly and often exceed what can be obtained from diet alone, especially in later trimesters. Supplementation has proven effective in controlled settings, but large-scale success is limited by poor compliance and weak healthcare systems. Preventive approaches and novel delivery methods offer some promise, yet long-term food fortification remains the most practical and cost-effective solution [5]. This article emphasizes the risks of nutrient deficiencies during pregnancy, particularly iron, and the importance of dietary supplementation. Deficiencies can lead to complications like miscarriage and preterm delivery. Personalized prenatal care is key, with prolonged-release ferrous sulfate recommended for its better safety profile and improved compliance [25].

II. DIETARY AND FORTIFIED NUTRITIONAL INTERVENTIONS

A systematic review was conducted to evaluate the effectiveness of dietary strategies, such as iron-rich or fortified foods, multi-nutrient intake, and

nutritional counseling, in preventing and treating iron-deficiency anemia in pregnant women. These interventions were found to be generally effective; however, the presence of moderate to high bias in many studies indicates the need for more rigorous randomized controlled trials [1]. This study aimed to assess the impact of a micronutrient-fortified beverage containing 11 essential nutrients on the nutritional status of pregnant women in Tanzania. In a randomized controlled trial involving 259 women, 8 weeks of supplementation led to significant improvements, including a 4.16 g/L increase in hemoglobin and a 3 g/L rise in ferritin levels. The intervention reduced the risk of anemia by 51%, iron deficiency anemia by 56%, and iron deficiency by up to 92%, indicating that such a fortified beverage could serve as an effective and practical preventive strategy during pregnancy [6]. This study explored how food intake affects hepcidin levels and the risk of gestational iron-deficiency anemia (IDA). It found that higher consumption of dim sum and dark leafy vegetables increased hepcidin levels, while higher carbohydrate intake and rice/porridge increased IDA risk. Vitamin C intake reduced the risk of IDA associated with vegetable consumption [20].

2. IRON SUPPLEMENTATION STRATEGIES

2.1 DAILY VS WEEKLY SUPPLEMENTATION:

Esther Casanueva at.al. (2005) conducted a study to compare the effects of daily and weekly iron supplementation in non-anemic pregnant women on hemoglobin levels, iron status, and pregnancy outcomes. Both supplementation methods effectively prevented anemia, with daily dosing showing greater effectiveness in reducing mild anemia and hypoferritinemia. However, the daily regimen was associated with a higher incidence of hemo concentration, which was linked to an increased risk of low birth weight and premature delivery [2]. Eva-Charlotte Ekström et.al. conducted a study in Bangladesh to compare weekly and daily iron supplementation during pregnancy, considering compliance. Daily supplementation showed a slightly greater improvement in hemoglobin levels, though most of the effect occurred within the first 20 tablets. With high compliance in the weekly group, the overall difference was minimal, suggesting that current iron dosage recommendations during pregnancy may be higher than necessary [3]. This study aimed to assess different iron supplementation strategies during pregnancy to prevent iron deficiency and associated side effects. Daily supplementation provides better protection against iron depletion, while intermittent supplementation offers fewer side effects and better compliance. Although no single approach is universally ideal, a moderate-dose iron protocol is likely to provide the most effective and balanced solution for pregnant women [9]. This study sought to assess the impact and quality of evidence for daily and intermittent iron or iron-folate supplementation on maternal anemia during pregnancy, following CHERG guidelines. The findings revealed that daily supplementation with iron or iron-folate led to a 73% reduction in anemia at term, supported by moderate-quality evidence. However, the effect on iron deficiency anemia was less consistent, and intermittent supplementation showed no significant benefit over daily regimens [12].

2.2. DOSAGE AND TIMING CONSIDERATIONS:

This study aimed to assess the effect of a 20 mg/day iron supplement on maternal iron deficiency anemia (IDA) and iron deficiency (ID) during pregnancy and postpartum. Results showed that supplementation from 20 weeks of gestation until delivery significantly reduced IDA (3% vs. 11%) and ID (35% vs. 58%) at delivery, with no significant difference in gastrointestinal side effects between the groups. At 6 months postpartum, the iron deficiency remained lower in the supplemented group (16% vs. 29%), although IDA rates were similar [7]. This study aimed to examine the influence of iron status on iron absorption during pregnancy by measuring supplemental iron absorption, red blood cell iron incorporation, and iron status in pregnant women. The results showed that supplementation with 60 mg Fe significantly increased serum ferritin, folate, and serum iron compared to the control group, while serum zinc levels were lower in the supplemented groups. Although iron absorption was inversely related to maternal serum ferritin, the difference in absorption between groups was not significant. These findings highlight the importance of prenatal iron supplementation for meeting iron requirements during pregnancy [8]. The study aimed to assess the impact of 100 mg/day iron supplementation during pregnancy on zinc absorption and status. It was found that zinc absorption increased in late pregnancy, and iron supplementation had no adverse effect on zinc status [10]. The study aimed to evaluate the effects of daily prenatal iron-folate supplementation on

maternal and neonatal iron status in rural China. The results showed that supplementation improved maternal hemoglobin levels and reduced the risk of anemia and iron deficiency, but a high proportion of both mothers and newborns still had iron deficiency at birth [11].

2.3. SUPPLEMENT FORMS AND COMPARATIVE EFFICACY:

This study compared the efficacy and safety of oral iron (III) polymaltose complex and ferrous sulfate in pregnant women with iron-deficiency anemia. Over 90 days, both treatments led to similar improvements in hemoglobin levels, but the polymaltose group had significantly higher ferritin levels and fewer side effects. These findings suggest that iron (III) polymaltose complex is as effective as ferrous sulfate and better tolerated for managing iron-deficiency anemia during pregnancy [21].

3. FACTORS INFLUENCING SUPPLEMENTATION EFFECTIVENESS;

3.1. COMPLIANCE AND ADHERENCE:

A study in Bangladesh compared daily and weekly iron supplementation during pregnancy, focusing on adherence. Daily intake slightly improved hemoglobin levels more than weekly doses, though most of the effect appeared within the first 20 tablets. With good adherence in the weekly group, the overall difference was minor, indicating that current iron dosage guidelines might be higher than required [3]. The study aimed to examine the factors contributing to persistent anemia in pregnant women in Chandigarh, India, with a focus on their knowledge, practices, and access to IFA tablets. Results showed that 65% were anemic, and only 35% received free IFA. Despite knowing the importance of green leafy vegetables, only 8% consumed them daily. Barriers like food insecurity, low decision-making power, and IFA stock-outs were significant challenges hindering proper nutrition and IFA use [15]. The study aimed to assess the impact of using direct observers to monitor iron supplementation adherence among pregnant women in a rural area of Belgaum, India. Results showed that the group with direct observers had higher adherence rates and improved hemoglobin levels compared to the control group. While no significant difference was observed in hemoglobin levels during the first two visits, a statistically significant difference of 0.57 g/dL was noted in the 4th visit, highlighting the effectiveness of direct observation in improving compliance with iron supplementation [17].

3.2. Healthcare System and Policy Contexts: The study aimed to explore the prevalence and management of iron deficiency and anemia among pregnant women in France. It found that nearly 60% of women were at moderate or significant risk of iron deficiency, with an overall anemia prevalence of 15.8%, which increased with pregnancy duration. Iron-based medication was prescribed to 57.3% of patients. The results indicate that in French clinical practice, the risk of iron deficiency and anemia during pregnancy aligns with expectations and is managed according to national and international guidelines [4]. The study aimed to explore the prevalence and management of iron deficiency and anemia among pregnant women in France. It found that nearly 60% of women were at moderate or significant risk of iron deficiency, with an overall anemia prevalence of 15.8%, which increased as pregnancy progressed. Iron-based medications were prescribed to 57.3% of patients, aligning with national and international guidelines for managing these conditions during pregnancy [16]. This update by the U.S. Preventive Services Task Force aimed to evaluate whether screening and routine iron supplementation in pregnant women and adolescents improves maternal and infant health outcomes. After reviewing available evidence, the USPSTF concluded that there is insufficient data to determine the balance of benefits and harms for both screening and routine iron supplementation in asymptomatic pregnant women to prevent adverse health or birth outcomes [24].

3.3. Monitoring and Observation Techniques:

A study in rural Belgaum, India, evaluated the role of direct observers in monitoring iron supplement adherence during pregnancy. Women under observation showed better compliance and higher hemoglobin levels than those without supervision. Although early visits showed no major differences, a notable increase of 0.57 gm% in hemoglobin was recorded during the fourth visit, emphasizing the benefit of direct monitoring [17].

4. Nutrient Interactions and Micronutrient Synergy;

The study by Soroku Nishiyama (1999) aimed to investigate the relationship between zinc (Zn) status, zinc supplementation, and their effects on insulin-like growth factor-I (IGF-I) and iron deficiency anemia in pregnant women. The results showed that combining zinc with iron supplementation significantly improved hemoglobin levels, red blood cell counts, and reticulocyte numbers. Additionally, IGF-I levels increased and were positively correlated with improvements in hemoglobin and red blood cells. The findings suggest that zinc status plays a role in hematological abnormalities during pregnancy, with Zn-derived IGF-I influencing hematopoiesis [19]. The study aimed to assess whether 25(OH) vitamin D (colecalciferol) status is linked to ferritin levels and anemia during pregnancy. The results showed that 95.5% of subjects had low colecalciferol, with 75.5% being deficient. Although anemia was found in only 7.5% of subjects, it increased by trimester in colecalciferol-deficient women. No significant association was found between colecalciferol levels and ferritin or anemia, but ferritin and pre-pregnancy BMI were correlated with anemia in the first trimester, and anemia in the second trimester strongly predicted anemia in the third trimester [14]. This study analyzed NHANES data (1999–2006) to assess supplement use and folate status among 1296 pregnant women in the U.S. While 77% reported taking supplements, mainly folic acid and iron, usage was lowest (55–60%) in the first trimester and increased in later stages. RBC folate levels were higher in supplement users and rose with each trimester. Despite folic acid's importance in early pregnancy, its low intake in the first trimester highlights a gap in early prenatal care [22]. A study analyzing data from 1296 pregnant women in NHANES (1999–2006) assessed folic acid and iron supplement use along with RBC folate status. About 77% reported supplement use, but only 55% did so in the first trimester. RBC folate levels were higher in supplement users and increased with pregnancy progression. The lowest folate levels and supplement use were observed in early pregnancy, emphasizing the need for improved compliance with folic acid recommendations during the first trimester [23].

5. Special Conditions and Regional Concerns

5.1. Malaria-Endemic Areas:

The study assessed the safety and effectiveness of iron supplementation during pregnancy in malaria-endemic regions. It found that iron supplementation did not increase the risk of placental malaria or affect birth weight. However, it significantly improved hemoglobin and serum ferritin levels, reduced anemia by 40%, and decreased maternal iron deficiency by 52%, along with a 66% reduction in iron deficiency anemia [18].

5.2. Rural and Low-Income Settings:

A study conducted in rural China examined the impact of daily prenatal iron-folate supplementation on maternal and newborn iron levels. The findings revealed improved maternal hemoglobin and reduced risk of anemia and iron deficiency; however, a significant number of both mothers and infants remained iron-deficient at birth [11]. The study intended to assess the impact of prenatal nutritional assistance on anemia and vitamin A deficiency (VAD) by comparing pre-intervention and intervention groups. The results showed that the intervention significantly reduced anemia and night blindness prevalence, with anemia decreasing from 28.4% to 16.8% and night blindness from 18.7% to 6.2%, demonstrating a positive effect on maternal health [13]. A study in Chandigarh, India, explored factors contributing to persistent anemia in pregnant women, focusing on knowledge, practices, and access to IFA tablets. The results revealed that 65% of women were anemic, and only 35% had access to free IFA. Despite recognizing the importance of green leafy vegetables, only 8% consumed them daily. Key challenges included food insecurity, limited decision-making power, and frequent IFA stock-outs [15].

6. Novel Approaches and Personalized Prenatal Care;

Iron requirements during pregnancy significantly increase, often surpassing what can be obtained from diet alone, particularly in the later trimesters. While supplementation is effective in controlled environments, large-scale success is hindered by poor adherence and weak healthcare systems. Although innovative delivery methods and preventive strategies show promise, long-term food fortification remains the most cost-effective and practical solution. This article highlights the risks of nutrient deficiencies, especially iron, during pregnancy and underscores the importance of dietary supplementation. Iron deficiency can lead to complications like miscarriage and preterm birth. Personalized prenatal care, along with prolonged-

release ferrous sulfate, is recommended for better safety and improved adherence [25]. The study by Soroku Nishiyama investigated the link between zinc (Zn) levels, zinc supplementation, and their impact on insulin-like growth factor-I (IGF-I) and iron deficiency anemia in pregnant women. The findings revealed that zinc supplementation alongside iron significantly enhanced hemoglobin levels, red blood cell counts, and reticulocyte numbers. Furthermore, IGF-I levels increased, showing a positive correlation with improvements in hemoglobin and red blood cell counts. The results suggest that zinc plays a key role in addressing hematological issues during pregnancy, with Zn-derived IGF-I contributing to hematopoiesis [19].

CONCLUSION

Anemia during pregnancy remains a significant global health concern, with iron deficiency being its most common cause. The review highlights that both biotechnological advancements, such as the use of recombinant erythropoietin (rEPO), and nutritional strategies, including iron-rich diets and fortified supplements, play vital roles in anemia prevention and management. While dietary interventions and iron supplementation have shown consistent benefits in improving maternal hemoglobin levels and reducing anemia-related complications, the use of rEPO offers a promising therapeutic option, especially in severe or unresponsive cases. However, challenges such as compliance, accessibility, and the need for personalized approaches still persist. Moving forward, integrated strategies combining medical innovation with public health nutrition policies are essential to effectively address anemia in pregnant women and ensure better maternal and fetal outcomes.

REFERENCES

[1] Skolmowska D., Effectiveness of Dietary Interventions in Prevention and Treatment of Iron-Deficiency Anemia in Pregnant Women: A Systematic Review of Randomized Controlled Trials, *Nutrients* 2022, 14(15), 3023; https://doi.org/10.3390/nu14153023

[2] Casanueva E. et al., Weekly Iron as a Safe Alternative to Daily Supplementation for Nonanemic Pregnant Women, *Elsevier Inc.*, doi: 10.1016/j.arcmed.2005.11.011

[3] Eva-Charlotte Ekström, SM Ziauddin Hyder, A Mushtaque R Chowdhury, Sadia A Chowdhury, Bo Lönnerdal, Jean-Pierre Habicht, and Lars Åke Persson, Efficacy and Trial Effectiveness of Weekly and Daily Iron Supplementation among Pregnant Women in Rural Bangladesh: Disentangling the Issues, *Am J Clin Nutr* 2002;76:1392–1400.

[4] Thierry Harvey, Asmaa Zkik, Marie Auges & Thierry Clavel, Assessment of Iron Deficiency and Anemia in Pregnant Women: An Observational French Study, *Womens Health* (2016) 12(1), 95–102.

[5] Thomas H. Bothwell, Iron Requirements in Pregnancy and Strategies to Meet Them, *Am J Clin Nutr* 2000;72(suppl):257S–64S.

[6] Diklar Makola, Deborah M. Ash, Simon R. Tatala, Michael C. Latham, Godwin Ndossi, Haile Mehansho, A Micronutrient-Fortified Beverage Prevents Iron Deficiency, Reduces Anemia and Improves the Hemoglobin Concentration of Pregnant Tanzanian Women, *Am J Nutr Sci* 2003.

[7] Maria Makrides, Caroline A Crowther, Robert A Gibson, Rosalind S Gibson, and C Murray Skeaff, Efficacy and Tolerability of Low-Dose Iron Supplements during Pregnancy: A Randomized Controlled Trial, *Am J Clin Nutr* 2003;78:145–53.

[8] Kimberly O O'Brien, Nelly Zavaleta, Laura E Caulfield, Dong-Xiao Yang, and Steven A Abrams, Influence of Prenatal Iron and Zinc Supplements on Supplemental Iron Absorption, Red Blood Cell Iron Incorporation, and Iron Status in Pregnant Peruvian Women, *Am J Clin Nutr* 1999;69:509–15.

[9] John L Beard, Effectiveness and Strategies of Iron Supplementation during Pregnancy, *Am J Clin Nutr* 2000;71(suppl):1288S–94S.

[10] Linda J Harvey, Jack R Dainty, Wendy J Hollands, Victoria J Bull, Jurian A Hoogewerff, Robert J Foxall, Liadhan McAnena, JJ Strain, and Susan J Fairweather-Tait, Effect of High-Dose Iron Supplements on Fractional Zinc Absorption and Status in Pregnant Women, *Am J Clin Nutr* 2007;85:131–6.

[11] Gengli Zhao, Guobin Xu, Min Zhou, Yaping Jiang, Blair Richards, Katy M Clark, Niko Kaciroti, Michael K Georgieff, Zhixiang Zhang, Twila Tardif, Ming Li, Betsy Lozoff, Prenatal Iron Supplementation Reduces Maternal Anemia, Iron Deficiency, and Iron

Deficiency Anemia in a Randomized Clinical Trial in Rural China, but Iron Deficiency Remains Widespread in Mothers and Neonates, *J Nutr* 2015;145:1916–23.

[12] Mohammad Yawar Yakoob, Zulfiqar A Bhutta, Effect of Routine Iron Supplementation with or without Folic Acid on Anemia during Pregnancy, *BMC Public Health* 2011, 11(Suppl 3):S21.

[13] C. Barbosa Chagas, A. Ramalho, P. de Carvalho Padilha, B. Della Libera, and C. Saunders, Reduction of Vitamin A Deficiency and Anemia in Pregnancy after Implementing Proposed Prenatal Nutritional Assistance, *Nutr Hosp.* 2011;26:843-850.

[14] RadenTinaDewiJudistiani, LaniGumilang, Sefita Aryuti Nirmala, Setyorini Irianti, Deni Wirhana, Irman Permana, Liza Sofjan, Hesty Duhita, Lies Ani Tambunan, Jeffry Iman Gurnadi, UmarSeno, ReniGhrahani, Agnes RenggaIndrati, Yunia Sribudiani, Tetty Yuniati, Budi Setiabudiawan, Association of Colecalciferol, Ferritin, and Anemia among Pregnant Women: Result from Cohort Study on Vitamin D Status and Its Impact during Pregnancy and Childhood in Indonesia, *Hindawi Anemia*, Volume 2018, Article ID 2047981.

[15] Nadia G. Diamond-Smith, Madhu Gupta, Manmeet Kaur, Rajesh Kumar, Determinants of Persistent Anemia in Poor, Urban Pregnant Women of Chandigarh City, North India: A Mixed Method Approach, *Food and Nutrition Bulletin* 2016, Vol. 37(2), 132-143.

[16] Thierry Harvey, Asmaa Zkik, Marie Auges & Thierry Clavel, Assessment of Iron Deficiency and Anemia in Pregnant Women: An Observational French Study, *Womens Health* (2016) 12(1), 95–102.

[17] Anil Bilimale, Javad Anjum, H.N. Sangolli, Mahesh Mallapur, Improving Adherence to Oral Iron Supplementation during Pregnancy, *Australasian Medical Journal* 2010, 3(5), 281-290.

[18] Analee J. Etheredge, ZulPremji, NilupaS.Gunaratna, AjibolaIbraheemAbioye, SaidAboud, ChristopherDuggan, Robert Mongi, DonnaSpiegelman, DrucillaRoberts, DavidsonH.Hamer, WafaieW.Fawzi, Iron Supplementation in Iron-Replete and Nonanemic Pregnant Women in Tanzania: A Randomized Clinical Trial, *JAMA Pediatr.*, doi:10.1001/jamapediatrics.2015.1480.

[19] Soroku Nishiyama, MD, FACN, Kohji Kiwaki, MD, Yoshinobu Miyazaki, MD, Taiji Hasuda, Zinc and IGF-I Concentrations in Pregnant Women with Anemia before and after Supplementation with Iron and/or Zinc, *American College of Nutrition*, Vol. 18, No. 3, 261–267 (1999).

[20] Noor Rohmah Mayasari, Chyi-Huey Bai, Tzu-Yu Hu, Jane C.-J. Chao, Ya Li Huang, Fan-Fen Wang, Alexey A. Tinkov, Anatoly V. Skalny, and Jung-Su Chang, Yi Chun Chen, Associations of Food and Nutrient Intake with Serum Hepcidin and the Risk of Gestational Iron-Deficiency Anemia among Pregnant Women: A Population-Based Study, *Nutrients* 2021, 13, 3501.https/doi.org/10.3390/nu13103501

[21] Ricardo Ortiz, Jorge Eduardo Toblli, Juan Diego Romero, Beatriz Monterrosa, Cristina Frer, Eugenia Macagno & Christian Breymann, Efficacy and Safety of Oral Iron(III) Polymaltose Complex versus Ferrous Sulfate in Pregnant Women with Iron-Deficiency Anemia: A Multicenter, Randomized, Controlled Study, *The Journal of Maternal-Fetal and Neonatal Medicine*, 2011, 1-6.

[22] Amy M. Branum, Regan Bailey, Barbara J. Singe, Dietary Supplement Use and Folate Status during Pregnancy in the United States, *American Society for Nutrition*, 2013.

[23] Rafał Kocyłowski, Iwona Lewicka, Mariusz Grzesiak, Zuzanna Gaj, Anna Sobańska, Joanna Poznaniak, Constantin von Kaisenberg, Joanna Sulibursk, Assessment of Dietary Intake and Mineral Status in Pregnant Women, *Archives of Gynecology and Obstetrics* (2018) 297:1433–1440.

[24] Albert L. Siu, MD, MSPH, on behalf of the U.S. Preventive Services Task Force, Screening for Iron Deficiency Anemia and Iron Supplementation in Pregnant Women to Improve Maternal Health and Birth Outcomes: U.S. Preventive Services Task Force Recommendation Statement, *Ann Intern Med.* 2015;163:529-536. doi:10.7326/M15-1707

[25] Nils Milman, Tomasz Paszkowski, Irene Cetin, Camil Castelo-Branco, Supplementation during Pregnancy:Beliefs and Science, *Gynecol Endocrinol.* 2016 Jul;32(7):509-16.doi: 10.3109/09513590.2016.1149161.