Iron-Containing Oral Contraceptives

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Oral contraceptive use has been associated with decreased menstrual blood losses; thus, can independently reduce the risk of anemia and iron deficiency in women. Manufacturers have recently started to include supplemental iron in the non-hormonal placebo tablets of some contraceptives.

Keywords: iron ; ferrous iron ; ferritin ; iron deficiency ; iron-containing oral contraceptives ; hemoglobin ; anemia ; oral contraceptive ; contraceptive ; birth control

1. Introduction

Contraceptives are an unparalleled innovation in the public health sector, allowing for family planning and pregnancy prevention [1], with estimates of 922 million users worldwide [2]. Contraceptives can be categorized into two methods: hormonal and non-hormonal contraception. The former includes contraception methods, such as hormonal intrauterine devices (IUD), oral contraceptive pills, and the vaginal ring [3]. The latter consists of barrier methods (male or female condom, with or without spermicide), copper IUD, the withdrawal method [3], and fertility awareness-based methods (FAM) [4], characterized by observing the physical signs that change throughout the different phases of a woman's menstrual cycle along with hormone fluctuations to predict and monitor the fertile and infertile days. The importance of universal access to family planning education and services is underscored by the global commitment made in the Sustainable Development Goal target 3.7.1—that by 2030, access to sexual and reproductive healthcare services could be ensured to all, and that reproductive health be integrated into national strategies and programs [5].

Based on the data compiled for the report Contraceptive Use by Method 2019 by the United Nations, approximately 16% of women use oral contraceptives [2]. This report is based on data from 1247 surveys collected between 1950 and 2018 in 195 countries among women of reproductive age, defined as 15 to 49 years of age. Commonly known as the birth control pill or "the pill," oral contraceptives are widely used. Reported rates of use among women are approximately 19% in Europe, 17% in Oceania, 15% in North America, 15% in Latin America, and 5% in Asia [2]. Oral contraceptives typically contain varying levels of both estrogen and progesterone (known as 'combined contraceptives'), or solely progesterone [1][6]. With proper use, the effectiveness of oral contraceptives to prevent pregnancy can be up to 99%, though this is rarely achieved due to the challenge of remembering to consume it at the same time each day [6]. The physiological mechanism of oral contraceptive pills includes preventing the release of an egg from the ovaries, thickening the cervical mucus (making it harder for sperm to reach the uterus), and thinning the uterine lining to stop the uterus implantation of a fertilized egg [6].

Generally, oral contraceptives come in packets of 21 hormonal tablets followed by seven inactive placebo tablets. These placebo pills are void of any medical benefits and are given to mimic natural menses through a withdrawal bleed, while allowing women to continue the habit of consuming one tablet daily.

Beyond pregnancy prevention, women also use oral contraceptives for other reasons, as the synthetic hormones included in oral contraceptives have been shown to have other positive health benefits [7]. Some women consume oral contraceptives to manage acne, menstrual cramps, or heavy menstrual bleeding [6]. Heavy blood loss from menstruation is a potential contributor to iron deficiency anemia [8]. Defined as a blood loss of ~80 mL during one menstrual cycle [9], studies have shown that heavy menstrual bleeding affects ~18–38% of women of reproductive age [10]. However, the proportion of women thought to experience heavy menstrual bleeding is likely even higher due to underdiagnosis [10]. Prolonged heavy menstrual blood may lead to decreased iron stores in women, especially if women are not consuming a sufficient amount of dietary iron [10].

Oral contraceptives are known to reduce the duration and amount of menstrual blood loss throughout the menstrual cycle, potentially resulting in lower menstrual iron losses [11]. Interestingly, oral contraceptive users have been shown to have higher serum iron levels compared to non-oral contraceptive users [12][13][14][15]. In a population survey of 676 premenopausal Danish women (>35 years of age), serum ferritin concentrations were found to be inversely associated with the duration of menses ($p < 0.0001$) [15]. Further, in the same study, the duration of menses for women consuming oral contraceptives was shorter than those not consuming oral contraceptives, and median serum ferritin concentrations were ~62 μg/L vs. ~42 μg/L, respectively [15]. In another study of 268 healthy, menstruating, non-pregnant Danish women aged 18–30 years, serum ferritin concentrations were also observed to be inversely correlated with the duration of menstruation (spearman's rank correlation coefficient (rs) = −0.25, $p < 0.001$) and perceived menstrual bleeding intensity (rs = −0.27, $p < 0.001$). Interestingly, some data suggest that oral contraceptive use may negatively impact a woman's vitamin B_6 status. Vitamin B_6 is a cofactor in heme synthesis; however, a causal relationship between oral contraceptive use and anemia has not been established [16]. Further, women using oral contraceptives had a significantly shorter duration of menstruation than those using other methods of contraception, including IUDs [14]. In conclusion, there is strong evidence that oral contraceptives are associated with iron stores in women of reproductive age and have the potential to decrease monthly menstrual blood losses and directly impact the iron status of women.

Some manufacturers have recently started to include supplemental iron in place of the placebo tablets typically included (consumed during the week of the withdrawal bleed) with the goal of reducing the risk of anemia and iron deficiency among women. Iron is an essential mineral required for red blood cell production and oxygen transportation [17]. Iron deficiency is one of the most common nutritional deficiencies in the world [18]; it is characterized by low iron stores and is diagnosed by a ferritin concentration below a defined cut-off for a specific population [18]. Meeting dietary iron requirements is critical for women of reproductive age as they experience monthly iron losses during menstruation [10][19]. Iron deficiency anemia is common among women of reproductive age and can increase the risk of negative pregnancy outcomes [20] and impair work capacity [21]. There is strong evidence for the efficacy of iron supplementation to prevent and treat iron deficiency in both high and low-income countries [22]. In 2016, the World Health Organization issued a guideline recommending daily iron and folic acid (IFA) supplementation (30–60 mg elemental iron daily) for all menstruating adolescents and women for three consecutive months of the year in regions where anemia prevalence is ≥40% [23]. These recommendations are based on the presumption that iron deficiency causes ~50% of the global burden of anemia [23]. As a result of these international policies, iron supplements are widely distributed to women in many countries across the globe. To our knowledge, iron-containing oral contraceptives (ICOC) are currently available in North America [24][25][26][27][28][29][30][31][32][33][34], South Asia [35][36][37], West Asia [38], Southeast Asia [39][40][41], and Africa [42]. Yet, there is limited evidence to support the inclusion of this micronutrient in oral contraceptives; further, there are no data evaluating whether the inclusion of iron in ICOC is warranted or safe in iron-replete women.

2. Current Insights on Iron-Containing Oral Contraceptives

In certain populations and/or settings, ICOC has the potential to be a cost-effective alternative or addition to large-scale untargeted iron supplementation programs among women. As women of reproductive age are at risk for iron deficiency anemia [18][43], combining birth control and iron supplementation together can address both issues of family planning and iron deficiency anemia, with one cost-effective solution. Gebremedhin et al., in their paper on contraceptive use and Hb concentration in sub-Saharan Africa, also noted the potential of ICOC to contribute to anemia reduction [44]. In addition, acceptance rates for ICOC would likely be high, as women are already used to taking their daily pill and would not need to change their routines. Oral contraceptives have also been used as a vehicle to deliver other micronutrients, including folic acid, to increase blood folate concentrations in women of reproductive age to reduce the risk of neural tube defects [45].

On the contrary, there could also be potential harms of untargeted population-wide iron supplementation through the provision of ICOC; therefore, both the benefits and harms must be evaluated. The tolerable upper intake level (UL) (the highest average daily micronutrient intake level unlikely to increase risk of adverse health effects to most individuals in a certain population group) for iron is 45 mg/day for non-pregnant women aged 19–50 years, on account of the commonly experienced side effects of iron supplementation, such as gastrointestinal discomfort [46]. Although the common dose of elemental iron found in the ICOC was 25 mg, not exceeding the UL, it still has the potential to cause gastrointestinal discomfort, and at worst, iron overload in some at-risk individuals (e.g., those with severe genetic hemoglobin disorders). In iron-replete individuals, the consumption of high-dose oral iron may be harmful. This is because iron is a catalyst for oxidative and inflammatory reactions. Consuming excess iron can result in free iron, called non-transferrin-bound iron, which can increase reactive oxygen species production, leading to oxidative stress [47][48] and DNA and cellular damage [49][50][51]. Excess iron has been associated with diabetes and neuropathy [52][53]; while decreased growth [54], impaired development [55][56], and increased morbidity have been observed in infants and children [57]. In malaria-endemic regions, iron supplementation is known to increase the risk of infection [58]. Excess iron that is not absorbed in the duodenum passes into the colon, where it has been demonstrated to increase the susceptibility to pathogen growth and intestinal inflammation in child and infant populations [59][60][61]. The risk of adverse effects of iron supplementation appears to be highest among populations with a high enteric burden and those with poor water, sanitation, and hygiene standards [62].

Lastly, the opportunity for iron supplementation to cause injury may pose a greater risk to populations with certain genetic hemoglobin disorders, which are autosomal inherited conditions, such as sickle cell disease or hemoglobin E disorder, common in many areas of the world [63]. In the case of severe forms of these genetic hemoglobin disorders, iron metabolism may be altered, putting women at higher risk of iron overload [63]. Therefore, not all women may benefit from ICOC, even if the population has high prevalence rates of anemia.

Of note, in all brands of ICOC that we discovered, the daily dose of elemental iron did not exceed 25 mg, and the iron-containing supplements in the ICOC are only consumed up to a total of seven days each month; thus, the risk of consuming ICOC still appear relatively low, even for those women that are iron-replete or have genetic hemoglobin disorders. As red blood cells have a ~120 lifespan, it is unknown if seven days of 25 mg elemental iron would be sufficient to improve depleted iron stores in women with severe iron deficiency anemia [17]. However, in some populations or regions, women may be consuming supplemental iron from other iron interventions (such as iron and folic acid, in line with the WHO recommendations), fortified food products, and ICOC. Under these circumstances, women may be at risk as they are consuming supplemental iron from multiple sources.

The most common form of iron included in the identified ICOC was ferrous fumarate. Iron salts, including ferrous fumarate, are poorly absorbed [64]. Certain dietary components affect the bioavailability of iron by binding it in the gastrointestinal tract, inhibiting its absorption. Staple foods in low-resource settings are often low in highly bioavailable heme iron (e.g., meat) and high in iron inhibitors (e.g., phytates found in cereals, legumes, and leafy greens) [17]. Chelated iron, such as ferrous bisglycinate (used in ICOC Balcoltra®), has been shown to have greater bioavailability in oral supplementation and food fortification than conventional iron salts and results in less gastrointestinal side effects [65][66]. Future research assessing the inclusion of iron in oral contraceptives should query the most appropriate form of iron for inclusion.

Lastly, ICOC are not currently included in the WHO Model Essential Medicines List (MEML). This list is used to guide the selection of medicines, including nutritional supplements, for the primary health care needs of the population [67]. If a formulation is included on this list, it suggests that it should be available (or approved for procurement), in adequate amounts, at the appropriate dosage and price, within a working health care system [68]. While ICOC are not included on the WHO MEML, oral contraceptives (30 µg ethinyl estradiol + 150 µg levonorgestrel; 35 µg ethinyl estradiol + 1 mg norethisterone; 30 µg levonorgestrel; and 30 µg ulipristal (as acetate)), iron and folic acid (equivalent to 60 mg iron + 400 micrograms folic acid) and iron-only (equivalent to 60 mg iron) tablets are listed. If future research shows ICOC to be an effective method to prevent and/or treat iron deficiency and/or anemia, it may be important to include ICOC in the WHO MEML to ensure ICOC are approved for procurement and have adequate supply.

3. Conclusions

Here, we discovered 21 different brands of ICOC that are currently being manufactured and marketed globally by 12 pharmaceutical companies. The daily dose of elemental iron in ICOC ranged from ~10–25 mg, with the most common dose being 25 mg. Very little research has been conducted to evaluate the effects of ICOC on biomarkers of anemia and iron status. Only one trial was identified in our search that compared the effects of ICOC to non-ICOC on Hb concentration and iron status in anemic women. There were no differences in Hb or serum iron concentrations among women receiving the ICOC and non-ICOC following 12 months of intervention. Therefore, no additional benefits of ICOC were observed; however, of note, adverse side effects were not assessed [69]. Despite this lack of evidence, numerous pharmaceutical companies continue to manufacture and distribute ICOC globally.

In some populations and/or settings, ICOC have the potential to be a cost-effective solution for the prevention and/or treatment of iron deficiency, which is one of the most common nutritional deficiencies globally [18]. Given that 16% of contraceptive users adopt the pill method, and menstruating women are known to be at risk of iron deficiency [2], women could potentially benefit from the inclusion of iron in oral contraceptives as a novel approach to address iron deficiency, as an alternative to iron or IFA supplementation or fortification programs. Still, research is warranted to assess the effectiveness of ICOC to increase Hb concentration and iron status, with the goal of preventing and/or treating iron deficiency. Considering the global widespread use of oral contraceptives, a rigorous elevation of both the benefits and harms of ICOC is needed, particularly in women who are iron-replete or have severe genetic hemoglobin disorders.

References

1. Cleland, J.; Conde-Agudelo, A.; Peterson, H.; Ross, J.; Tsui, A. Family Planning 2: Contraception and health. Lancet 2012, 380, 149–156.
2. United Nations. Contraceptive Use by Method 2019: Data Booklet; United Nations: Geneva, Switzerland, 2019.
3. Britton, L.E.; Alspaugh, A.; Greene, M.Z.; McLemore, M.R. CE: An evidence-based update on contraception. Am. J. Nurs. 2020, 120, 22–33.
4. Urrutia, R.P.; Polis, C.B. Fertility awareness based methods for pregnancy prevention. BMJ 2019, 366.
5. United Nations Goal 3|Department of Economic and Social Affairs. Available online: (accessed on 4 June 2021).
6. Frye, C.A. An overview of oral contraceptives: Mechanism of action and clinical use. Neurology 2006, 66, 29–36.
7. Dhont, M. Non-contraceptive benefits of oral contraceptives. Open Access J. Contracept. 2011, 2, 119–126.
8. Camaschella, C. Iron-deficiency anemia. N. Engl. J. Med. 2015, 372, 1832–1843.
9. Sriprasert, I.; Pakrashi, T.; Kimble, T.; Archer, D.F. Heavy menstrual bleeding diagnosis and medical management. Contracept. Reprod. Med. 2017, 2, 1–8.
10. Mansour, D.; Hofmann, A.; Gemzell-Danielsson, K. A review of clinical guidelines on the management of iron deficiency and iron-deficiency anemia in women with heavy menstrual bleeding. Adv. Ther. 2021, 38, 201–225.
11. Lethaby, A.; Wise, M.R.; Weterings, M.A.J.; Rodriguez, M.B.; Brown, J. Combined hormonal contraceptives for heavy menstrual bleeding. Cochrane Database Syst. Rev. 2019, 2019.
12. Yeasmin, T.; Haque, M.S.; Yeasmin, S.; Amin, M.R. Iron status in women using oral contraceptives. Bangladesh J. Physiol. Pharmacol. 2014, 26, 25–29.
13. Hasanat, F.; Chakroborty, P.; Hasanat, A.; Sharmin, S.; Mannan, M.; Nargis, S. Status of serum iron and copper in women taking oral contraceptive. Bangladesh J. Med. Biochem. 2018, 10, 5–9.
14. Milman, N.; Clausen, J.; Byg, K.E. Iron status in 268 Danish women aged 18–30 years: Influence of menstruation, contraceptive method, and iron supplementation. Ann. Hematol. 1998, 77, 13–19.
15. Milman, N.; Rosdahl, N.; Lyhne, N.; Jørgensen, T.; Graudal, N. Iron status in Danish women aged 35–65 years: Relation to menstruation and method of contraception. Acta Obstet. Gynecol. Scand. 1993, 72, 601–605.
16. Wilson, S.M.C.; Bivins, B.N.; Russell, K.A.; Bailey, L.B. Oral contraceptive use: Impact on folate, vitamin B 6, and vitamin B 12 status. Nutr. Rev. 2011, 69, 572–583.
17. Lynch, S.; Pfeiffer, C.M.; Georgieff, M.K.; Brittenham, G.; Fairweather-Tait, S.; Hurrell, R.F.; McArdle, H.J.; Raiten, D.J. Biomarkers of nutrition for development (BOND)- Iron review. J. Nutr. 2018, 148, 1001S–1067S.
18. Camaschella, C. Review Series: Iron metabolism and its disorders—Iron deficiency. Blood 2019, 133, 30–39.
19. Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on iron and its importance for human health. J. Res. Med. Sci. 2014, 19, 164–174.
20. World Health Organization. Worldwide Prevalence of Anaemia 1993–2005; World Health Organization: Geneva, Switzerland, 2008.
21. Haas, J.D.; Brownlie, T., IV. Iron deficiency and reduced work capacity: A critical review of the research to determine a causal relationship. J. Nutr. 2001, 131, 676S–690S.
22. Low, M.S.Y.; Speedy, J.; Styles, C.E.; De-Regil, L.M.; Pasricha, S.R. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. Cochrane Database Syst. Rev. 2016, 2016.
23. World Health Organization. Guideline: Daily Iron Supplementation in Adult Women and Adolescent Girls; WHO: Geneva, Switzerland, 2016.
24. Low Estrogen Birth Control|Lo Loestrin® Fe. Available online: (accessed on 4 June 2021).
25. Lo Minastrin Fe. Available online: (accessed on 4 June 2021).
26. FDA. CDER Lo/Ovral-28* and Ferrous Fumarate Tablets (Norgestrel and Ethinyl Estradiol Tablets and Ferrous Fumarate Tablets). Available online: (accessed on 4 June 2021).
27. FDA. CDER Taytulla. Available online: (accessed on 4 June 2021).
28. FDA. CDER ESTROSTEP Fe. Available online: (accessed on 4 June 2021).
29. Balcoltra®. Available online: (accessed on 4 June 2021).
30. Hailey Fe 1/20—FDA Prescribing Information, Side Effects and Uses. Available online: (accessed on 4 June 2021).

31. MICROGESTIN® (Norethindrone Acetate and Ethinyl Estradiol Tablets, USP). Available online: (accessed on 4 June 2021).
32. Norminest® Fe Tablets. Available online: (accessed on 4 June 2021).
33. Loestrin® 24 Fe. Available online: (accessed on 4 June 2021).
34. FDA. CDER MinastrinTM 24 Fe. Available online: (accessed on 4 June 2021).
35. Suvida—The Best Oral Contraceptive Pill—EskagPharma. Available online: (accessed on 4 June 2021).
36. Government of India. Reference Manual for Oral Contraceptive Pills Family Planning; Division Ministry of Health and Family Welfare: New Delhi, India, 2016.
37. Incepta Pharmaceuticals|A Leading Pharmaceutical Company in Bangladesh. Available online: (accessed on 4 June 2021).
38. Teva's Generic of Loestrin® 21 Tablets: Junel® 1/20 (Norethindrone Acetate and Ethinyl Estradiol Tablets, USP). Available online: (accessed on 4 June 2021).
39. Prescription Medications—Charlize®. Available online: (accessed on 4 June 2021).
40. Trust Pill Full Prescribing Information, Dosage & Side Effects|MIMS Philippines. Available online: (accessed on 4 June 2021).
41. World Health Organization. Zinnia F: Patient Information Leaflet; WHO: Geneva, Switzerland, 2015.
42. Levofem. Available online: (accessed on 4 June 2021).
43. Lopez, A.; Cacoub, P.; Macdougall, I.C.; Peyrin-Biroulet, L. Iron deficiency anaemia. Lancet 2016, 387, 907–916.
44. Gebremedhin, S.; Asefa, A. Association between type of contraceptive use and haemoglobin status among women of reproductive age in 24 sub-Saharan Africa countries. BMJ Sex. Reprod. Health 2019, 45, 54–60.
45. Shere, M.; Bapat, P.; Nickel, C.; Kapur, B.; Koren, G. The effectiveness of folate-fortified oral contraceptives in maintaining optimal folate levels to protect against neural tube defects: A systematic review. J. Obstet. Gynaecol. Can. 2015, 37, 527–533.
46. Otten, J.J.; Hellwig, J.P.; Meyers, L.D. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements; National Academies Press: Washington, DC, USA, 2006; ISBN 978-0-309-15742-1.
47. Schümann, K.; Kroll, S.; Weiss, G.; Frank, J.; Biesalski, H.K.; Daniel, H.; Friel, J.; Solomons, N.W. Monitoring of hematological, inflammatory and oxidative reactions to acute oral iron exposure in human volunteers: Preliminary screening for selection of potentially-responsive biomarkers. Toxicology 2005, 212, 10–23.
48. Schümann, K.; Ettle, T.; Szegner, B.; Elsenhans, B.; Solomons, N.W. On risks and benefits of iron supplementation recommendations for iron intake revisited. J. Trace Elem. Med. Biol. 2007, 21, 147–168.
49. Brissot, P.; Ropert, M.; Le Lan, C.; Loréal, O. Non-transferrin bound iron: A key role in iron overload and iron toxicity. Biochim. Biophys. Acta 2011, 169, 403–410.
50. Mollet, I.G.; Dilipkumar, P.; Govani, F.S.; Giess, A.; Paschalaki, K.; Periyasamy, M.; Lidington, E.C.; Mason, J.C.; Jones, M.D.; Game, L.; et al. Low dose iron treatments induce a DNA damage response in human endothelial cells within minutes. PLoS ONE 2016, 11, e0147990.
51. Aksu, B.Y.; Hasbal, C.; Himmetoglu, S.; Dincer, Y.; Koc, E.E.; Hatipoglu, S.; Akcay, T. Leukocyte DNA damage in children with iron deficiency anemia: Effect of iron supplementation. Eur. J. Pediatr. 2010, 169, 951–956.
52. Li, K.; Reichmann, H. Role of iron in neurodegenerative diseases. J. Neural Transm. 2016, 123, 389–399.
53. Hansen, J.B.; Moen, I.W.; Mandrup-Poulsen, T. Iron: The hard player in diabetes pathophysiology. Acta Physiol. 2014, 210, 717–732.
54. Lind, T.; Seswandhana, R.; Persson, L.-Å.; Lönnerdal, B. Iron supplementation of iron-replete Indonesian infants is associated with reduced weight-for-age. Acta Paediatr. Int. J. 2008, 97, 770–775.
55. Lozoff, B. Iron deficiency and child development. Food Nutr. Bull. 2007, 28, S560–S571.
56. Lozoff, B.; Castillo, M.; Clark, K.M.; Smith, J.B. Iron-fortified vs low-iron infant formula: Developmental outcome at 10 years. Arch. Pediatr. Adolesc. Med. 2012, 166, 208–215.
57. Dewey, K.G.; Domellöf, M.; Cohen, R.J.; Rivera, L.L.; Hernell, O.; Lönnerdal, B. Iron supplementation affects growth and morbidity of breast-fed infants: Results of a randomized trial in Sweden and Honduras. J. Nutr. 2002, 132, 3249–3255.

58. Sazawal, S.; Black, R.E.; Ramsan, M.; Chwaya, H.M.; Stoltzfus, R.J.; Dutta, A.; Dhingra, U.; Kabole, I.; Deb, S.; Othman, M.K.; et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: Community-based, randomised, placebo-controlled trial. Lancet 2006, 367, 133–143.

59. Jaeggi, T.; Kortman, G.A.M.; Moretti, D.; Chassard, C.; Holding, P.; Dostal, A.; Boekhorst, J.; Timmerman, H.M.; Swinkels, D.W.; Tjalsma, H.; et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut 2015, 64, 731–742.

60. Paganini, D.; Zimmermann, M.B. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: A review. Am. J. Clin. Nutr. 2017, 106, 1688S–1693S.

61. Paganini, D.; Uyoga, M.A.; Kortman, G.A.M.; Cercamondi, C.I.; Moretti, D.; Barth-Jaeggi, T.; Schwab, C.; Boekhorst, J.; Timmerman, H.M.; Lacroix, C.; et al. Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: A randomised controlled study in Kenyan infants. Gut 2017, 66, 1956–1967.

62. Dostal, A.; Baumgartner, J.; Riesen, N.; Chassard, C.; Smuts, C.M.; Zimmermann, M.B.; Lacroix, C. Effects of iron supplementation on dominant bacterial groups in the gut, faecal SCFA and gut inflammation: A randomised, placebo-controlled intervention trial in South African children. Br. J. Nutr. 2014, 112, 547–556.

63. Zimmermann, M.B.; Fucharoen, S.; Winichagoon, P.; Sirankapracha, P.; Zeder, C.; Gowachirapant, S.; Judprasong, K.; Tanno, T.; Miller, J.L.; Hurrell, R.F. Iron metabolism in heterozygotes for hemoglobin E (HbE), α-thalassemia 1, or β-thalassemia and in compound heterozygotes for HbE/β-thalassemia. Am. J. Clin. Nutr. 2008, 88, 1026–1031.

64. Tondeur, M.C.; Schauer, C.S.; Christofides, A.L.; Asante, K.P.; Newton, S.; Serfass, R.E.; Zlotkin, S.H. Determination of iron absorption from intrinsically labeled microencapsulated ferrous fumarate (sprinkles) in infants with different iron and hematologic status by using a dual-stable-isotope method. Am. J. Clin. Nutr. 2004, 80, 1436–1444.

65. Youssef, A.M.; Shata, A.F.; Kamal, H.M.; El-saied, Y.; Ali, O.F. A comparative study of efficacy, tolerability, and compliance of oral iron preparations for iron deficiency anemia in pregnant women. Am. J. Med. Med. Sci. 2014, 4, 244–249.

66. Milman, N.; Jønsson, L.; Dyre, P.; Pedersen, P.L.; Larsen, L.G. Ferrous bisglycinate 25 mg iron is as effective as ferrous sulfate 50 mg iron in the prophylaxis of iron deficiency and anemia during pregnancy in a randomized trial. J. Perinat. Med. 2014, 42, 197–206.

67. World Health Organization. WHO|Essential Medicines. Available online: (accessed on 4 June 2021).

68. Roche, M.L.; Samson, K.L.I.; Green, T.J.; Karakochuk, C.D.; Martinez, H. Perspective: Weekly iron and folic acid supplementation (WIFAS): A critical review and rationale for inclusion in the essential medicines list to accelerate anemia and neural tube defects reduction. Adv. Nutr. 2021, 12, 334–342.

69. Rivera, R.; Almonte, H.; Arreola, M.; Iqez, F.; Mcnarrez, G.; Navarro, C.; Perkin, G.W.; Ruiz, R. The effects of three different regimens of oral contraceptives and three different intrauterine devices on the levels of hemoglobin, serum iron and iron binding capacity in anemic women. Contraception 1983, 27, 311–327.