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Iron therapy in obstetrics and gynaecology: a review

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There are three problems in managing iron deficiency anaemia in child-bearing-age women: lack of awareness of the condition by both patient and clinician, inexperience in the diagnosis, and lack of familiarity with available oral and intravenous iron therapy. Iron deficiency is common in women, from menarche, through growth spurt in puberty, pregnancy, and postpartum, and until menopause. To screen for underlying iron deficiency, a haemoglobin cut-off for anaemia is used. Iron deficiency anaemia must be excluded for patients with haemoglobin level below the cut-off. Oral iron therapy is effective in treating iron deficiency anaemia. Low-dose alternate-day oral iron therapy is recommended (rather than daily iron dose). It is crucial to accompany oral iron therapy with vitamin C. Intravenous iron therapy, particularly with third-generation iron compounds, is safe, effective, and faster acting than oral iron therapy.

Keywords: Anemia, iron-deficiency; Ferritins; Postpartum period; Pregnancy

Introduction

Iron is vital for bodily functions. Women typically have 2000-3000 mg elemental iron in the body (about 40 mg/kg). Two-thirds of the body's iron is embedded in red blood cells facilitating oxygen transfer, whereas 10% is in skeletal muscle and the myocardium carrying out oxidative metabolism or in iron-containing enzymes and proteins all over the body involved in adenosine triphosphate formation, DNA synthesis, hormonal synthesis, signal-controlling functions in neurotransmitters, and detoxification in the liver. The remaining iron is stored in the reticuloendothelial system. Well-nourished child-bearing-age women retain around 300-600 mg (5-10 mg/kg) iron in this reticuloendothelial system. A normal pregnancy requires around 1000 mg elemental iron[1,2]. This requirement would be challenging for women with low iron reserve because of inadequate dietary iron intake and/or high menstrual flow.

Epidemiology

Iron deficiency anaemia affects one-sixth of the global population (ie around 1.24 billion people)[3]. It ranks the fourth in the leading causes of disability worldwide[3]. In Hong Kong, there are no epidemiological data about anaemia, iron deficiency, or iron deficiency anaemia in child-bearing-age women. According to data from new blood donors, the anaemic rate among reproductive age women increased from 21.6% in adolescents aged 16-20 years to 26.9% in women aged 41-50 years (Table 1). According to data from local hospitals, 16.3% of women are anaemic at term and 22.3% of women are anaemic post-delivery (Table 2).

Clinical consequences of iron deficiency

Iron deficiency anaemia markedly impairs the quality of life in child-bearing-age women and may result in fatigue, reduced exercise tolerance, reduced concentration, and impaired emotional control manifesting as depression, anxiety, stress or irritability, restless leg syndrome, and hair loss[4-6]. During pregnancy there may be additional detrimental effects on maternal and fetal outcomes. In a retrospective study of 75 660 singleton pregnancies, 7977 women were diagnosed with iron deficiency anaemia at delivery. Compared with pregnant women without iron deficiency, the presence of iron deficiency increased the risks of blood transfusion (odds ratio [OR]=5.48, 95% confidence interval [CI]=4.57-6.58), preterm delivery (OR=1.54, 95% CI=1.36-1.76), Caesarean delivery (OR=1.30, 95% CI=1.13-1.49), 5-minute Apgar score <7 (OR=2.21, 95% CI=1.84-2.64), and intensive care unit admission (OR=1.28, 95% CI=1.20-1.39)[2,7]. In a meta-analysis of 26 studies, maternal anaemia (mostly iron deficiency anaemia) was associated with higher risks of low birthweight (relative risk [RR]=1.31, 95% CI=1.13-1.51), preterm birth (RR=1.63, 95% CI=1.33-2.01), perinatal mortality (RR=1.51, 95% CI=1.30-1.76), and neonatal mortality (RR=2.72, 95% CI=1.19-6.25)[2,8].

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Table 1. Anaemia rate in new female blood donors in 2016 and 2017 (n=57 312)

Anaemia (haemoglobin level, g/dL)	Anaemia rate in new female blood donors, %			
	Age 16-20 years	Age 21-30 years	Age 31-40 years	Age 41-50 years
Severe (<8.0)	0.2	0.2	0.3	0.6
Moderate (8.0-10.9)	6.8	6.8	8.1	10.4
Mild (11.0-12.0)	14.6	15.8	16.0	15.9
Total	**21.6**	**22.8**	**24.4**	**26.9**

Table 2. Anaemia rate at admission and at discharge in women who deliver in Hospital Authority hospitals in September 2018 (n=2668)

Haemoglobin level, g/dL	No. (%) of women	
	At admission	At discharge
<7.0	4 (0.1)	3 (0.1)
7.0-7.9	15 (0.6)	62 (2.3)
8.0-8.9	57 (2.1)	197 (7.4)
9.0-9.9	195 (7.3)	333 (12.5)
10.0-10.5	163 (6.1)	-
Total	**434 (16.3)**	**595 (22.3)**

Diagnosis

To screen for underlying iron deficiency, different haemoglobin level cut-offs for anaemia at different stages of women's life have been defined[9]. The cut-off of <12 g/dL in non-pregnant women is widely accepted[9]. However, cut-offs in pregnant women are diverse: <11 g/dL is suggested by the World Health Organization (WHO)[9]; <11 g/dL in the first trimester and <10.5 g/dL in second and third trimesters are suggested by the British Committee for Standards in Haematology (BCSH)[10], the Royal College of Obstetricians and Gynaecologists (RCOG)[11], the National Institute for Health and Care Excellence (NICE)[12], the American College of Obstetricians and Gynecologists (ACOG)[13], and in South Australia[14]. For the postpartum period, BCSH defines anaemia as <10.0 g/dL[10], whereas Milman defined anaemia as <10 g/dL within 24-48 hour after delivery, <11 g/dL at first week postpartum, and <12 g/dL at 8 weeks postpartum and beyond[15,16].

To exclude iron deficiency in women with haemoglobin level below cut-offs, oral iron therapy trial is recommended for confirmation of iron deficiency anaemia[10,11,13,14,17]. Serum ferritin should be measured, as it is the most reliable indicator of iron deficiency in the absence of inflammation. The WHO defines iron deficiency as serum ferritin of <15 ng/mL[18]; however, the BCSH definition of <30 ng/mL is more widely accepted, improves sensitivity from 25% to 92%, and maintains specificity at 98%[10]. To accurately assess the maternal iron store, measuring serum ferritin at the first prenatal visit and at the beginning of the third trimester in addition to the usual haemoglobin checking is recommended[2]. Iron therapy is recommended if serum ferritin <40 ng/mL in the presence of anaemia or serum ferritin <15 ng/mL in the absence of anaemia[2]. In women with or suspected to have thalassemia trait or other haemoglobinopathy, concomitant iron deficiency can be diagnosed by either oral iron therapy trial or measurement of serum ferritin levels if haemoglobin levels are below cut-off[2].

Oral iron therapy

Prophylactic oral iron therapy is recommended throughout child-bearing age (by the WHO)[19,20], during pregnancy (by the WHO[21], Centers for Disease Control and Prevention [CDC][17], Network for the Advancement of Transfusion Alternatives [NATA][22]), and during postpartum (by the WHO[5] and NATA[22]). Oral iron therapy trial in the presence of anaemia is recommended as confirmation for iron deficiency anaemia (by the CDC[17], BCSH[10], RCOG[11], ACOG[13], and in South Australia[14]). Most international clinical guidelines agree that oral iron therapy is the first-line therapy for confirmed iron deficiency anaemia, except in some clinical scenarios in which oral iron therapy fails. Haemoglobin level should be rechecked after 4 weeks to confirm the response; a haemoglobin rise of at least 1 g/dL is considered optimal. Oral iron therapy should be continued until the haemoglobin level is normalised and continued for a few more months to restore the body iron reserve.

Recently, an important change in practice has been emphasised: to stop using daily iron dosing and start using low-dose alternate-day oral iron therapy[2]. This is based on the latest absorption studies that maximal absorption of iron occurs with a dose in the range of 40-80 mg of elemental iron daily and that greater doses do not result in more iron

absorption and are associated with more side effects[23,24]. Once-daily and twice-daily regimens are comparable in terms of fractional (day 1-3 geometric mean: 11.8% [range, 7.1%-19.4%] once daily vs 13.1% [range, 8.2%-20.7%] twice daily, p=0.33) or total iron absorption (day 1-3: 44.3 mg [range, 29.4-66.7 mg] once daily vs 49.4 mg [range, 35.2-69.4 mg] twice daily, p=0.33)[25]. Twice-daily divided doses resulted in a higher serum hepcidin concentration than once-daily dosing (p=0.013) and reduces iron absorption; iron supplements on alternate days and in single doses optimise iron absorption[25].

In addition, administration of 250 mg of vitamin C with low-dose oral iron therapy increases oral iron absorption by 4-6 times[1,2,26-30]. The effect of vitamin C on iron absorption is so significant that it can be considered one of the physiological roles of vitamin C[1]. Nonetheless, multivitamins that contain both calcium and iron should never be used as iron therapy, because calcium inhibits most iron absorption in this setting[31].

Intravenous iron therapy

The wider application of intravenous (IV) iron therapy has reshaped management of iron deficiency anaemia in gynaecology and obstetrics settings. Blood transfusion was previously regarded as inevitable for patients in whom oral iron therapy was ineffective. However, each unit of red cell contains only around 200 mg of elemental iron, 0.5 mg elemental iron per 1 mL blood, which means a large volume of blood is required to replenish the total body iron deficit. First-generation IV iron therapies (iron saccharide, high-molecular-weight dextran iron) are effective treatments for iron deficiency, but the dextran-induced anaphylactic reaction hampers wider use. Second-generation IV iron therapies (iron gluconate, iron sucrose) result in markedly fewer severe adverse events by replacing the dextran component with other non-dextran carbohydrates. Third-generation IV iron compounds (ferric carboxymaltose, iron isomaltoside, ferumoxytol) allow a larger dose of iron in a shorter infusion time owing to advancement in the carbohydrate moiety compounding the core iron[32]. These IV iron compounds behave as prodrugs and retain ionic iron until the iron–carbohydrate complex is metabolised[32].

Efficacy

In a meta-analysis of 10 605 patients treated with IV iron in 72 randomised controlled trials (19 of them related to obstetrics), intravenous iron therapy was associated with an increase in haemoglobin concentration (standardised mean difference=6.5 g/L, 95% CI=5.1-7.9 g/L) and a reduced risk of requirement for red blood cell transfusion (risk ratio=0.74, 95% CI=0.62-0.88) and could have broad applicability in acute care settings[33]. In another meta-analysis of 10 randomised controlled trials comparing IV iron with oral iron in treatment of iron deficiency anaemia in pregnancy, pregnant women were more likely to achieve target haemoglobin level with IV iron than prophylactic oral iron in seven studies (summary OR=2.7, 95% CI=2.0-3.6, p<0.001); haemoglobin levels increased more at 4 weeks with IV iron in eight studies (mean difference=1.2 g/dL, 95% CI=1.0-1.3 g/dL, p<0.001); and adverse reactions were lower with IV than prophylactic oral iron in 10 studies (summary OR=0.54, 95% CI=0.41-0.72, p<0.001)[34]. IV iron therapy is superior to oral iron therapy for iron deficiency anaemia in pregnancy; women receiving IV iron therapy achieve desired target haemoglobin levels, more frequently, faster, and with fewer side effects[34]. Within bone marrow, IV iron therapy results in 4.5-7.8 times the normal production of erythrocytes, compared with the 2.5-3.5 times in oral iron therapy[35].

Safety

In a study of 688 183 recipients of IV iron therapy under Medicare from January 2003 to December 2013, the risk for anaphylaxis at first exposure was 68 (95% CI=57.8-78.7) per 100 000 persons for iron dextran and 24 (95% CI=20.0-29.5) per 100 000 persons for all non-dextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol), with an adjusted OR of 2.6 (95% CI=2.0-3.3, p<0.001)[36]. In another meta-analysis of 10 390 patients treated with IV iron in 103 trials (27 of them related to obstetrics and gynaecology), IV iron therapy was associated with an estimated severe adverse reaction incidence of <1 in 200 000 when high-molecular-weight dextran iron was avoided[37]. However, red blood cell transfusion was associated with events that cause major morbidity in 1 in 21 413 components issued according to the Serious Hazards of Transfusion 2012 data[37]. There was no increased risk of infections with IV iron therapy; IV iron formulations are safe and can be an alternative to red blood cell transfusions[37]. A placental perfusion study reported that ferric carboxymaltose did not pass to the fetus via the placenta[38].

Cost-effectiveness

In a study comparing the cost-effectiveness of IV iron with prophylactic oral iron in treating severe iron deficiency anaemia, the cost of IV iron therapy was 29.30% lower than that of oral iron therapy; in patients with severe iron deficiency anaemia (haemoglobin of <8.0 g/dL), IV iron therapy is an effective, safe, and overall less expensive

iron delivery[39]. In another study comparing IV iron therapy with allogeneic blood transfusion for severely anaemic gynaecologic patients, the net saving was US$782 per capita for IV iron therapy[40]. A study in Greece comparing the cost-effectiveness of second- and third-generation IV iron therapies reported that the total cost of ferric carboxymaltose was 113% and 15.4% lower than that of iron sucrose and low-molecular-weight dextran iron, respectively, in an inpatient analysis, and was 201.1% and 151.8% lower in an outpatient analysis[41]. Ferric carboxymaltose is a cost-saving option compared with second-generation IV iron[41]. A study in Switzerland on the cost-effectiveness of various IV iron therapies reported that the third-generation IV iron (ferric carboxymaltose) was associated with cost savings of 30% to 44% per patient per treatment cycle, compared with second-generation IV iron (iron sucrose).[42] Costs per 200/500/1000 mg total dosage treatment cycle were reported to be US$101/210/420 for ferric carboxymaltose and US$144/375/721 for iron sucrose; substituting iron sucrose with ferric carboxymaltose results in cost savings of US$22-31 million across all indications in 2009[42].

Stratification

IV iron therapy in obstetrics and gynaecology is recommended in United Kingdom, Germany, Switzerland, Scandinavia, Spain, Eastern Europe, Russia, Pakistan, India, Malaysia, Singapore, Indonesia, China, Thailand, Peru, Argentina, Chile, Australia, and the United States[2,4,6,10-14,22,40,43-51]. IV iron therapy is considered when oral iron therapy fails or is expected to fail in the following clinical scenarios: oral iron therapy intolerance[2,4,6,10-14,22,40,43-47,49,50], oral iron therapy unresponsiveness[2,4,6,10-14,22,40,43-47,49,50], oral iron therapy non-compliance[2,4,6,10-14,22,40,43-47,49,50], known conditions causing absorption problems[2,4,6,10,11,13,14,40,43,47,49,50], excessive blood loss exceeding the rate of oral absorption capacity[4,45], severe anaemia[6,13,22,40,44,46,47,50,51], iron deficiency anaemia in the presence of risk factors such as coagulation disorders, placenta previa[6], third trimester[2,22,44], and close proximity to term or obstetric/gynaecological operations[4,6,11,14,22,43,44,49].

Although clinical scenarios vary individually, different regions have different recommendations for oral and IV iron therapy in pregnancy and postpartum (Table 3)[6,22,40,44,46,47].

Administration and dosage

Two preparations allow total dose infusion. Premedication is not necessary prior to IV iron therapy in patients without a history of asthma or drug allergy. In patients with asthma or more than one drug allergy who are at increased risk of allergic or infusion reaction, corticosteroid (eg intravenous hydrocortisone 100-500 mg) should be administered prior to IV iron therapy. In patients with a history of inflammatory arthritis, IV corticosteroid, followed by a short course of prednisone (1 mg/kg per day orally for 4 days), is suggested. These recommendations avoid adverse events secondary to premedications for IV iron therapy, especially diphenhydramine. Premedication with diphenhydramine may cause hypotension, somnolence, flushing, dizziness, irritability, nasal congestion, wheezing, and supraventricular tachycardia[52]. Patients should be monitored for adverse effects for at least 30 minutes following injection.

Iron isomaltoside is added to maximum 500 mL sterile 0.9% sodium chloride. Doses <1000 mg and >1000 mg must be infused for >15 minutes and >30 minutes, respectively. The maximum single dose is 20 mg/kg bodyweight. If split dose is required, 20 mg/kg bodyweight is given in the first dose and the second dose is given at least 1 week apart. In patients with bodyweight of 50-69

Table 3. Different recommendations for oral and intravenous (IV) iron therapy in pregnancy and postpartum[6,22,40,44,46,47]

Region	Haemoglobin level, g/dL	
	Oral iron therapy	IV iron therapy
Switzerland[40]		
Pregnancy	9-10.5	≤9
Postpartum	10-11.5	≤10
Germany[47]		
Pregnancy	9-11.5	≤9
Postpartum	8-10	≤8
Turkey[6]		
Pregnancy	9-11 (1st & 3rd trimesters); 9-10.5 (2nd trimester)	≤9
Postpartum	9-11	≤9
Asia-Pacific[46]		
Pregnancy	10-10.5	≤10
Postpartum	10-10.5	≤10
Network for the Advancement of Transfusion Alternatives[22,44]		
Pregnancy	≤11 (2nd trimester)	≤11 (3rd trimester)
Postpartum	-	≤10

kg and ≥70 kg, iron isomaltoside of 1500 mg and 2000 mg, respectively, is needed for haemoglobin of <10 g/dL, whereas 1000 mg and 1500 mg, respectively, is needed for haemoglobin of ≥10 g/dL[53].

Ferric carboxymaltose is added to maximum 250 mL sterile 0.9% sodium chloride. Its dilution and infusion time are similar to that of iron isomaltoside. The maximum single dose is 1000 mg. If split dose is required, 1000 mg is given in the first dose and the second dose is given at least 1 week apart. In patients with bodyweight of <35 kg, 35-69 kg, and ≥70 kg, ferric carboxymaltose of 500 mg, 1500 mg, and 2000 mg, respectively, is needed for haemoglobin of <10 g/dL; 500 mg, 1000 mg, and 1500 mg, respectively, is needed for haemoglobin of 10-13 g/dL; and 500 mg, 500 mg, and 500 mg, respectively, is needed for haemoglobin of ≥14 g/dL[54].

Contraindications

Contraindications include hypersensitivity to the intended intravenous iron, known serious hypersensitivity to other intravenous iron products, first trimester of pregnancy, non-iron deficiency anaemia (eg haemolytic anaemia), iron overload or disturbances in utilisation of iron (eg haemochromatosis, haemosiderosis), active infection, and decompensated liver disease[53,54].

Response monitoring

Haemoglobin level and iron parameters should be measured 4 to 8 weeks after IV iron therapy[55].

Conclusion

Iron deficiency anaemia should be managed by addressing the underlying cause of the iron deficiency and replenishing the iron store. Both oral and IV routes of iron therapy are safe and efficacious, even in complicated clinical scenarios.

Declaration

The author has no conflicts of interest to disclose.

References

1. World Health Organization, Food and Agricultural Organization of the United Nations. Vitamin and mineral requirements in human nutrition. 2nd edition; 2004.
2. Schantz-Dunn J, Barbieri RL. Recognize and treat iron deficiency anemia in pregnant women. OBG Manag 2017;29:8-11,16.
3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211-59. Crossref
4. Friedman AJ, Shander A, Martin SR, et al. Iron deficiency anemia in women: a practical guide to detection, diagnosis, and treatment. Obstet Gynecol Surv 2015;70:342-53. Crossref
5. Guideline: Iron supplementation in postpartum women. Geneva: World Health Organization; 2016.
6. Api O, Breyman C, Çetiner M, Demir C, Ecder T. Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: iron deficiency anemia working group consensus report. Turk J Obstet Gynecol 2015;12:173-81. Crossref
7. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. Transfusion 2015;55:2799-806. Crossref
8. Rahmann MM, Abe SK, Rahman MS, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr 2016;103:495-504. Crossref
9. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011.
10. Pavord S, Myers B, Robinson S, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2012;156:588-600. Crossref
11. Blood Transfusion in Obstetrics. Green-top Guideline No. 47. Royal College of Obstetricians and Gynaecologists; 2015.
12. Antenatal care for uncomplicated pregnancies (CG62). National Institute for Health and Care Excellence Clinical guideline; 2008.
13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: anemia in pregnancy. Obstet Gynecol 2008;112:201-7. Crossref
14. Clinical Guideline Anaemia in Pregnancy Policy developed by SA Maternal & Neonatal Community of Practice. Approved SA Health Safety & Quality Strategic Governance Committee on 19 April 2016.
15. Milman N. Postpartum anemia I: definition, prevalence, causes, and consequences. Ann Hematol 2011;90:1247-53. Crossref
16. Milman N. Postpartum anemia II: prevention and treatment. Ann Hematol 2012;91:143-54. Crossref
17. Recommendations to prevent and control iron deficiency in

the United States. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47:1-29.
18. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011.
19. Guideline: Daily iron supplementation in adult women and adolescent girls. Geneva: World Health Organization; 2016.
20. Guideline: Intermittent iron and folic acid supplementation in menstruating women. Geneva: World Health Organization; 2011.
21. Essential nutrition actions: improving maternal, newborn, infant and young child health and nutrition. Geneva: World Health Organization; 2013.
22. Muñoz M, Peña-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018;28:22-39. Crossref
23. 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;126:1981-9. Crossref
24. Schrier SL. So you know how to treat iron deficiency anemia. Blood 2015;126:1971. Crossref
25. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol 2017;4:e524-33. Crossref
26. Siegenberg D, Baynes RD, Bothwell TH, et al. Ascorbic acid prevents the dose-dependent inhibitory effects of polyphenols and phytates on nonheme-iron absorption. Am J Clin Nutr 1991;53:537-41. Crossref
27. Cook JD, Monsen ER. Vitamin C, the common cold, and iron absorption. Am J Clin Nutr 1977;30:235-41. Crossref
28. Hallberg L, Brune M, Rossander L. Effect of ascorbic acid on iron absorption from different types of meals. Studies with ascorbic-acid-rich foods and synthetic ascorbic acid given in different amounts with different meals. Hum Nutr Appl Nutr 1986;40:97-113.
29. Derman DP, Bothwell TH, MacPhail AP, et al. Importance of ascorbic acid in the absorption of iron from infant foods. Scand J Haematol 1980;25:193-201. Crossref
30. Hallberg L, Brune M, Rossander-Hulthén L. Is there a physiological role of vitamin C in iron absorption? Ann N Y Acad Sci 1987;498:324-32. Crossref
31. Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. Am J Med 2008;121:943-8. Crossref
32. Bhandari S, Pereira DIA, Chappell HF, Drakesmith H. Intravenous irons: from basic science to clinical practice. Pharmaceuticals (Basel) 2018;11. Crossref
33. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ 2013;347:f4822. Crossref
34. Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: systematic review and meta-analysis. Am J Perinatol 2018 [Epub ahead of print].
35. Hillman RS, Henderson PA. Control of marrow production by level of iron supply. J Clin Invest 1969;48:454-60. Crossref
36. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015;314:2062-8. Crossref
37. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 2015;90:12-23. Crossref
38. Malek A. In vitro studies of ferric carboxymaltose on placental permeability using the dual perfusion model of human placenta. Arzneimittelforschung 2010;60:354-61.
39. Alejandra L, Gustavo MH, Nelida P. Analysis of relative cost variations and relative effectiveness of anemia treatment via alternate methods of iron administration. J Health Care Finance 2016;42.
40. Selma A, Skupski B, Prasad N, Tsai T. Intravenous iron infusion as an alternative to blood transfusion in severely anemic gynecologic patients. Obstet Gynecol 2016;127:140S. Crossref
41. Fragoulakis V, Kourlaba G, Goumenos D, Konstantoulakis M, Maniadakis N. Economic evaluation of intravenous iron treatments in the management of anemia patients in Greece. Clinicoecon Outcomes Res 2012;4:127-34.
42. Brock E, Braunhofer P, Troxler J, Schneider H. Budget impact of parenteral iron treatment of iron deficiency: methodological issues raised by using real-life data. Eur J Health Econ 2014;15:907-16. Crossref
43. Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. Best Pract Res Obstet Gynaecol 2017;40:55-67. Crossref
44. Beris P, Maniatis A; NATA Working Group on Intravenous Iron Therapy. Guidelines on intravenous iron supplementation in surgery and obstetrics/gynecology. Transfus Altern Transfus Med 2007;9(Suppl 1):29.
45. Aetna Clinical Policy Bulletin Number: 0575. Intravenous iron therapy. Pennsylvania Medicaid; 2017.
46. Breymann C, Bian XM, Blanco-Capito LR, Chong C, Mahmud G, Rehman R. Expert recommendations for the diagnosis and treatment of iron-deficiency anemia during pregnancy and the postpartum period in the Asia-Pacific region. J Perinat Med 2011;39:113-21. Crossref
47. Bergmann RL, Dudenhausen JW, Ennen JC, et al. Diagnostik und Behandlung der Anamie und des Eisenmangels in der Schwangerschaft und im Wochenbett. Literaturuberblick und Empfehlungen [in German]. Geburtsh Frauenheilk 2009;69:682-6. Crossref
48. Breymann C, Honegger C, Holzgreve W, Surbek D. Diagnosis and treatment of iron-deficiency anaemia during pregnancy and postpartum. Arch Gynecol Obstet 2010;282:577-80. Crossref
49. Antenatal care anaemia: screening and management during pregnancy. Department of Health Western Australia 2015.

CMP 1.14.
50. Iron Deficiency Anaemia Clinical Practice Guideline | March 2018. Toward Optimized Practice. Alberta, Canada.
51. Intravenous iron for severe iron deficiency. Therapeutics Initiative. The University of British Columbia; 2016.
52. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica 2014;99:1671-6. Crossref
53. Package leaflet: Information for the user. Monofer® 100 mg/ml solution for injection/infusion. Pharmacosmos, Holbaek, Denmark.
54. Package leaflet: Information for the patient. Ferinject 50 mg iron/mL solution for injection/infusion (Ferric carboxymaltose). Vifor Pharma UK Limited, Surrey, UK.
55. Kitsati N, Liakos D, Ermeidi E, et al. Rapid elevation of transferrin saturation and serum hepcidin concentration in hemodialysis patients after intravenous iron infusion. Haematologica 2015;100:e80-3. Crossref