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Ironing Out the Details: How to Manage Anemia in Pregnancy in Women Living With CKD

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Chronic kidney disease (CKD) affects approximately 3% of pregnant women in high-income countries, and its prevalence is expected to increase due to rising maternal age, and the increasing prevalence of obesity and diabetes.[1] In low and middle-income countries the prevalence of CKD is likely higher, and whereas the initial stages of CKD are often undiagnosed in both settings, in low and middle-income countries, advanced kidney disease is more often diagnosed in pregnancy.[2] Managing women with CKD during pregnancy is therefore expected to become a more frequent global concern.

In this issue of Kidney International Reports, de Jong *et al.*[3] undertake a review of the available evidence pertaining to anemia in the context of pregnancy and CKD. Given that iron deficiency is the most frequent cause of anemia in pregnancy outside of the CKD context, the focus is mainly on this very frequent condition, that indeed is almost considered synonymous of anemia in the obstetric literature.

In this commentary, we outline some of the pathophysiological intricacies of practical relevance with regard to therapeutic interventions for correcting anemia in pregnant women with CKD.

Extrapolating from the pathophysiology of anemia in low-risk pregnancies to pregnant patients with CKD is not simple. First, targeted trials, or large observational studies in the CKD population are notably lacking. Second, CKD encompasses a broad spectrum of diseases, grades, stages, and treatments, including dialysis and kidney transplantation. Third, the pathogenesis of anemia in CKD is usually multifactorial. Fourth, the focus on anemia management is different. In low-risk pregnancies, the main cause of anemia is iron deficiency, followed by folic acid deficiency, in the absence of folic acid supplementation during pre-pregnancy.[4] Conversely, in advanced CKD, on dialysis and after kidney transplantation, the main focus is the erythropoietin deficiency, and the "iron issue" is mainly related to identifying the best ferritin target to meet erythropoiesis stimulating agent requirements.

As the review underlines, the definition of anemia changes in pregnancy: physiologic anemia, or "pseudo-anemia" of pregnancy, is due to hemodilution, characterized by a disproportionate increase of plasma volume (estimated at about 50%) compared to erythrocyte mass (estimated at 25%). Although the World Health Organization definition is the most frequently employed one, a few others are available (Table 1). Noteworthy, although a 0.5 to 1 g/dl hemoglobin (Hb) difference may seem insignificant in low-risk pregnancies, it significantly affects clinical management, especially in advanced CKD, in patients requiring erythropoiesis stimulating agents. Indeed, whereas in physiologic pregnancies the focus is on the definition of reference values, in patients with CKD, the few existing guidelines or best practices have tried to set pragmatic targets, and basically agree on targeting an Hb level above 10.5 to 11 g/dl, without setting a clear maximum acceptable level to guide pharmacologic interventions.

As brilliantly reviewed by de Jong *et al.*,[3] in physiological conditions the delicate interplay between erythropoietin, hepcidin, and erythroferrone is modulated by pregnancy, with an increase in erythropoietin, a decrease in hepcidin, and an increase in iron availability. Nonetheless, little is known about how reduced kidney tissue or impaired kidney function may affect these physiological adaptations.

Although, outside of the context of pregnancy, erythropoietin deficiency clinically appears only in late CKD stages, it is conceivable that the increase in

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Table 1. Anemia definition in pregnancy with and without chronic kidney disease, according to international guidelines

Reference	Definition of anemia and iron deficiency in pregnancy	Mentions
WHO, 2020[S1]	Hb < 11 g/dl	Does not differentiate Hb cutoffs through different pregnancy trimesters
WHO recommendations on antenatal care for a positive pregnancy experience, 2016[S2,S3]	T1, T3: < 11 g/dl; T2: < 10.5 g/d; ferritin < 15 μg/l (T1)	—
American College of Obstetricians and Gynecologists, 2021[S4]	T1: Hb < 11 g/dl; T2, T3: Hb < 10.5 g/dl; postpartum: < 10 g/dl; ferritin < 30 μg/l; TSAT < 16%	Hematocrit and Hb, lower cutoffs for T2, to reflect hemodilution (plasma volume expansion by 40%–50%)
UK guidelines on the management of iron deficiency in pregnancy, 2020[S5]	T1: Hb < 11 g/dl; T2, T3: Hb < 10.5 g/dl; postpartum: < 10 g/dl; ferritin <30 μg/l	A serum ferritin level of <30 μg/l in pregnancy is indicative of iron deficiency. Levels higher than this do not rule out iron deficiency
FIGO, 2019[S6]	Hb < 11 g/dl during pregnancy and postpartum	Unselected screening with routine use of serum ferritin is generally not recommended
Australian Red Cross Lifeblood[S7]	T3 Hb < 11 g/dl; T2 Hb < 10.5 g/dl; ferritin < 30 μg/l	With normal Hb and low ferritin, treat as if iron deficiency anemia
Iron Deficiency- British Columbia Guidelines- Diagnosis and Management Canada, 2019[S8]	T1 < 11 g/dl; T2, T3: Hb < 10.5 g/dl; ferritin < 30 μg/l	Hb increase by 1–2 g/dl in 4 wk. Continue iron 4–6/12 targeting a ferritin >100 μg/l
Royal College of Physicians of Ireland, 2019[S9]	T1: Hb < 11 g/dl; T2, T3: Hb < 10.5 g/dl; ferritin < 15 μg/l	—
Clinical Practice Guideline Board Iron in Pregnancy Auckland District Health New Zealand, 2015[S10]	Hb < 10 g/dl; ferritin < 15 μg/l	—
Asian Expert Consensus, 2023[S11]	T1, T3: Hb < 11g/dl; T2: Hb < 10.5 g/dl; ferritin < 15 μg/l; ferritin cutoff value is increased to < 70 μg/l in the context of inflammation or infection	Cutoff for ferritin established <15 μg/l, most likely because consensus panelist practice in resources limited settings
Anemia in pregnancy and CKD		
Dutch guideline, 2022[S12]	T1 < 11 g/dl; T2, T3 Hb < 10 g/dl; ferritin; stages 1–2: ≤ 80 μg/l; stages 3–5 ND: ≤ 200 μg/l; TSAT stages 3–5 ND: ≤ 30%	Not graded, expert opinion
UK guideline, 2019[S13]	10.5–11 g/dl; ferritin 1–2: ≤ 80 μg/l; TSAT stages 3–5 ND: < 20%	Not graded, expert opinion
Italian guideline, 2015[S14]	stage 5D, all trimesters Hb 10–11 g/dl; TSAT stages 5D: ≤ 30%	Not graded, expert opinion; guideline included; not graded, expert opinion; stages 5-5D
German guideline, 2022[S15]	Hb < 10–10.5 g/dl all trimesters	Not graded, expert opinion

CKD, chronic kidney disease; Hb, hemoglobin; ND, nondialysis; T1, trimester 1; T2, trimester 2; T3, trimester 3; TSAT, transferrin saturation; WHO, World Health Organization.

erythropoietin is blunted earlier, making anemia more evident also in earlier CKD phases.[5]

Increased maternal iron demands (the "magic number" in physiologic pregnancy is 1 g) are shared by both low-risk and high-risk pregnancies and are attributed to erythrocyte mass expansion, fetal requirements, and storage in reticulo-endothelial cells in the placenta.[5,6] Replenished iron stores are a requisite for optimizing the effects of erythropoietin; thus, the definition of iron deficiency in CKD has been set at a much higher level, namely at 100 μg/l, according to the recent Kidney Disease: Improving Global Outcomes controversy.[7] However, as de Jong *et al.*[3] note, even if iron deficiency definitions vary in physiological pregnancies (12–15 to 30–50 μg/l) these levels are much lower than those suggested in patients with CKD, even outside of the context of the increased demands of pregnancy.

Conversely, nephrology guidelines and best practices on pregnancy and kidney diseases attempted to apply in pregnancy, the well-established targets for patients with CKD.[S12–S15]

If iron supplementation were easy, this discussion would be pleonastic. However, the core issue regards the use of iron, and, in particular, of i.v. iron. Although oral iron can be taken without substantial contraindication in pregnancy, regardless of the presence of CKD, its gastrointestinal tolerance is not optimal, with frequent gastric intolerance, nausea (risking lowering food intake and, therefore, iron and vitamin intake), and constipation, leading to poor adherence.[8,S12]. Likewise, prescribing oral iron in patients with hyperemesis has not proven to be successful. Compliance is not high, mainly due to side effects, and the often-suggested alternate-day regimens may be even more difficult to follow, especially in the context of complex polypharmacy. Even in the absence of advanced CKD, iron stores are often low in our patients due to frequent blood sampling, and nutritional management which encourages normal or low intake of animal proteins that are richer in iron. In pregnancy, besides the frequent increase in the number of blood tests, the widespread use of aspirin for preeclampsia prevention (and, in selected cases, of

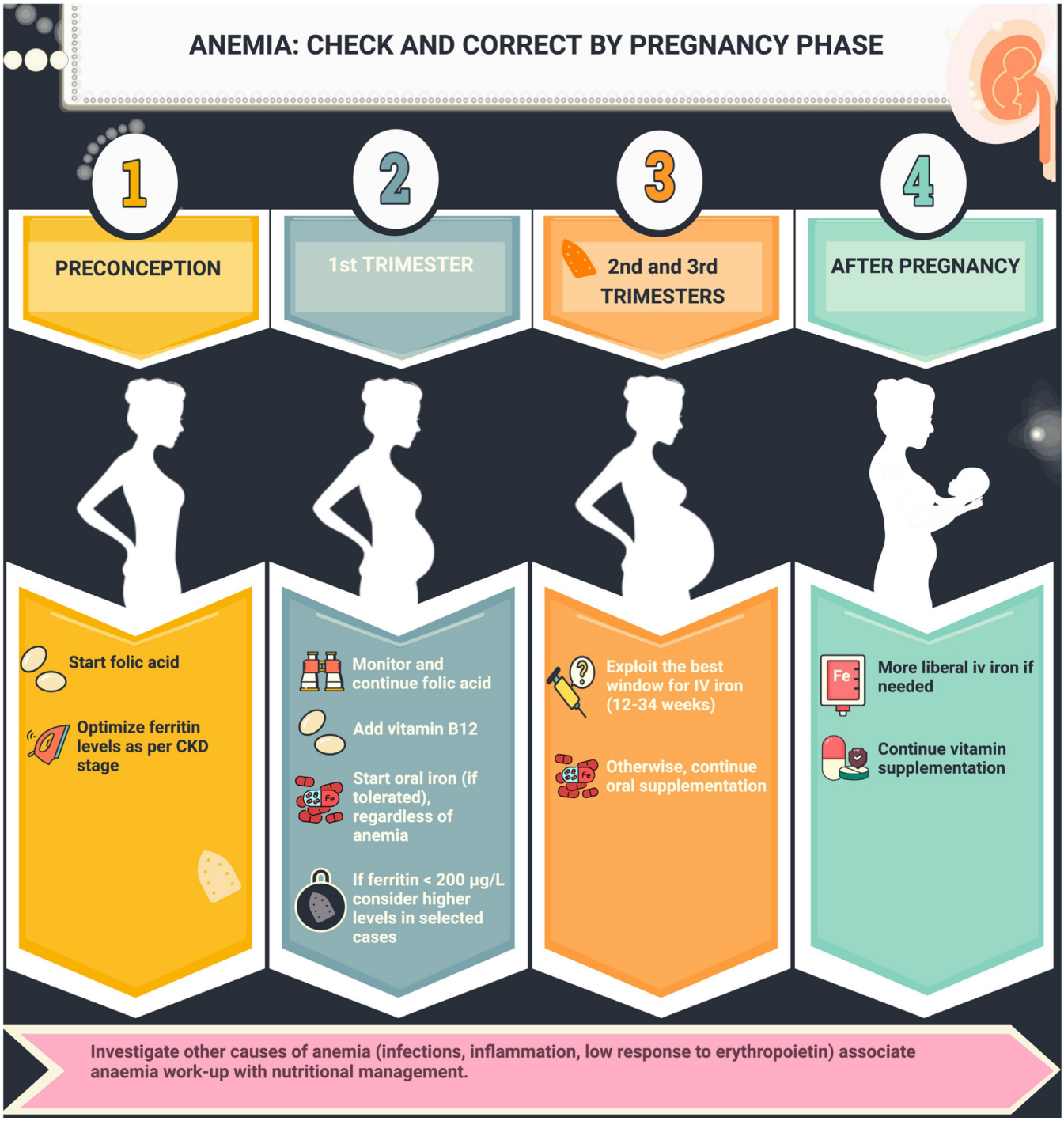

Figure 1. Anemia in pregnant women with chronic kidney disease: correcting anemia by pregnancy phase.

heparin, possibly combined with aspirin) may increase occult blood loss, adding to other causes of gastrointestinal loss (e.g., steroids and mucosal dysfunction).

Caution regarding the administration of i.v. iron in pregnancy is however always emphasized due to the fear of allergic reactions that can induce fetal bradycardia.[9,S16] Although bradycardia appears to be the result of maternal drug-related adverse effects, monitoring is generally advised during infusion, even with the new i.v. preparations (ferric carboxymaltose), for which allergic reactions are considered exceptional. Therefore, even if the risks are scaled back, logistical considerations may make timely treatment difficult.

Although the current review by de Jong *et al.*[3] wisely suggests considering the same Hb targets recommended for women without CKD, we may anticipate a response like that of the non-CKD population only in patients with CKD stage 1, without comorbidities

(including chronic inflammation, flares of an underlying disease, and treatment interference). Otherwise, it is difficult to expect that oral iron will suffice to control anemia in more advanced CKD, unless iron stores are already replenished at the much higher levels indicated for patients with CKD (ferritin over 100 μg/l, and up to 500 μg/l, if we consider the indications for patients treated with erythropoiesis stimulating agents).

In pregnancy, one of the main focuses is to avoid potentially harmful treatments, especially by minimizing i.v. iron use and avoiding blood transfusions; this holds true even more so in patients with CKD. Anemia is associated with all major pregnancy complications, many of which, including preterm delivery and delivery of small for gestational age babies, are also associated with pregnancy in patients with CKD.[S17] Furthermore, anemia is associated with adverse outcomes in CKD, dialysis, and kidney transplant patients, including graft loss in the latter group.[S18]

The cause-effect relationship is difficult to establish, because anemia may be the epiphenomenon of several pathologic conditions, especially in patients with CKD. Moreover, its prevalence is often related to poverty and is disproportionately higher in underserved individuals.

Although we agree that in pregnancy the adage "less is more" should apply to all treatments, there are at least 5 actions that could be suggested for patients with CKD, and that, though differing from obstetric guidelines, could improve outcomes without added risks (Figure 1).

The first action is to exploit the prepregnancy phase, at least in patients seeking preconception counseling. Detailed screening of the potential causes of anemia, including biochemical tests (besides those related to the underlying disease, should include blood cell count, iron, ferritin, transferrin saturation, inflammation markers, vitamin B12, folic acid, vitamin D, PTH, and thyroid hormones) may allow correcting metabolic problems and optimizing ferritin levels. If possible, a "nephrologic target" should be empirically set to a ferritin level between 100 and 500 μg/l, in the absence of inflammation. In this context, integrating oral and i.v. iron is possible, obviously preferring the drugs with the lowest risk for hypersensitivity reactions.

The second measure is to anticipate risk factors for anemia in pregnancy. The first evaluation during pregnancy of all patients with CKD should include a detailed assessment of potential risk factors for anemia, regardless of their Hb level at referral, following the above-mentioned indications. Timely correction of all potential causes of anemia may reduce future needs.

The third measure concerns replenishing iron stores. Even in cases first observed in pregnancy, and in those who have normal Hb levels, and ferritin levels in the normal-high range, starting oral iron supplementation may allow anticipating the future requirements. In fact, iron absorption is modulated by needs, and there is no risk of overload, and few severe side effects, the major limitations being poor tolerance and low therapeutic adherence.

The fourth measure is to integrate nutritional management with anemia management before, during, and after pregnancy. Malnutrition, an umbrella term that encompasses errors in nutrition (for example a diet based on ultraprocessed "empty" food), and low nutritional intake may be detrimental for kidney health and can be associated with protein wasting, a potential cause of anemia, especially in patients with late CKD stage or in individuals on dialysis. Furthermore, as de Jong *et al.*[3] underlined, potential vitamin B12 and iron deficiency in plant-based diets without proper management impact fetal growth. Conversely, these diets are associated with a lower incidence of small for gestational age and very preterm babies, in a context of strict control of nutritional markers, thus emphasizing the need for careful management.

The last measure is to exploit the best "treatment window." The best timing for i.v. iron supplementation is probably between 12 and 34 weeks, considering a possible teratogenic effect in animal models in the first trimester of gestation; whereas in the last weeks of gestation, higher iron levels could induce oxidative stress at birth. However, the existing evidence remains inconclusive.

In conclusion, managing anemia in pregnant women with CKD poses unique challenges. The complex nature of anemia in CKD, coupled with the lack of targeted trials and variability in treatment approaches, requires careful consideration. Simple measures such as preconception screening, anticipation of risk factors, replenishing iron stores, integrating nutritional management, and optimizing timing for i.v. iron supplementation can improve outcomes. However, further research is needed to establish clear guidelines for managing anemia in this population.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Piccoli GB, Alrukhaimi M, Liu ZH, Zakharova E, Levin A. World Kidney Day Steering Committee. Women and kidney disease: reflections on World Kidney Day 2018. *Kidney Int*. 2018;93:278–283. https://doi.org/10.1016/j.kint.2017.11.008
2. Ibarra-Hernandez M, Alcantar-Vallin ML, Soto-Cruz A, et al. Challenges in managing pregnancy in underserved women with chronic kidney disease. *Am J Nephrol*. 2019;49:386–396. https://doi.org/10.1159/000499964
3. de Jong MFC, Nemeth E, Rawee P, Bramham K, Eisenga MF. Anemia in pregnancy with CKD. *Kidney Int Rep*. 2024;9:1183–1197. https://doi.org/10.1016/j.ekir.2024.01.015
4. Fisher AL, Nemeth E. Iron homeostasis during pregnancy. *Am J Clin Nutr*. 2017;106(suppl 6):S1567–S1574. https://doi.org/10.3945/ajcn.117.155812
5. Morton A, Burke M, Morton A, Kumar S. Anaemia in chronic kidney disease pregnancy. *Obstet Med*. 2021;14:116–120. https://doi.org/10.1177/1753495X20948985
6. Cao C, O'Brien KO. Pregnancy and iron homeostasis: an update. *Nutr Rev*. 2013;71:35–51. https://doi.org/10.1111/j.1753-4887.2012.00550
7. Ku E, Del Vecchio L, Eckardt KU, et al. Novel anemia therapies in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int*. 2023;104:655–680. https://doi.org/10.1016/j.kint.2023.05.009
8. Sharma S, Smitha MV, Balakrishnan D. Telephonic intervention to combat non-adherence to oral iron-folic acid supplementation in pregnancy: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol X*. 2023;20:100235. https://doi.org/10.1016/j.eurox.2023.100235
9. Wong L, Smith S, Gilstrop M, et al. McClintock J, Auerbach M. Safety and efficacy of rapid (1,000 mg in 1 hr) intravenous iron dextran for treatment of maternal iron deficient anemia of pregnancy. *Am J Hematol*. 2016;91:590–593. https://doi.org/10.1002/ajh.24361