Iron Deficiency in Women's Health: An understated burden with serious health consequences

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Importance of iron

The importance of iron for overall health in humans cannot be overstated and its extremely widespread biological functions include electron transfer, intercellular signalling, catalysis, and oxygen binding and transport. Iron is found in all cells and is required for the synthesis of iron-sulphur clusters and heme proteins like cytochromes c, b5, and P450, myoglobin, neuroglobin and heme-based sensor proteins.[1] It is also an enzyme cofactor that is essential for many important biological processes, and studies have shown that up to 6.5% of all human enzymes are iron-dependant.[2]

The most widely known and appreciated function of iron is, however, that this seemingly unassuming element is a key component of the heme protein named haemoglobin (Hb), and responsible for binding oxygen and transporting it between the lungs and the rest of the body.[2,3] In each haemoglobin molecule, four heme groups, each with one iron atom attached to a porphyrin, surrounds a globin group consisting of two linked pairs of polypeptide chains.1 Each healthy haemoglobin molecule can accordingly bind four oxygen molecules. The majority of iron in circulation is used for erythropoiesis in the bone marrow, where up to three million red blood cells are produced every second. Any disruption in erythropoiesis due to the depletion of iron, will result is iron deficiency anaemia (IDA).[4]

Considering the extensive physiological role of iron, it is easily understood how iron deficiency (ID) and even iron deficiency without anaemia (IDWA) can lead to many vague and general symptoms like fatigue (most common), poor attention and other cognitive symptoms, poor work and physical performance, poor condition and healing of skin, nails and hair, hair loss and restless legs. In children problems like growth and developmental delay, poor appetite, and frequent infections are often reported.[5] It remains, however, difficult to separate the direct tissue effects of iron deficiency from the effects of iron deficiency anaemia via impaired oxygen delivery to all tissues and cardiovascular strain.[3]

Iron deficiency in women's health

Considering iron deficiency in women's health, there are several key considerations. IDA is the most common form of anaemia and research has shown that regardless of socio-economic background, women of reproductive age are particularly vulnerable to this nutritional deficiency.[6] Non-pregnant women with one or more of the following are specifically at high risk to have ID or IDA: heavy menstrual bleeding or abnormal uterine bleeding, heavy physical activity, frequently blood donation, and a history of gastrointestinal lesions.[6]

Among women with gynaecologic cancer, anaemia is particularly common. At diagnosis of several cancers associated with severe bleeding such as uterine body or cervical cancer, simple and severe IDA is the most common, but in many patients and later in the disease process anaemia is often multifactorial. Factors that play an important role include blood loss, para-neoplastic effects, kidney function impairment and reduced erythropoietin, nutritional and feeding difficulties, and bone marrow toxicity related to radiation and chemotherapy. Anaemia delays and interrupts treatment and has a direct and measurable negative effect on quality of life as well as general and cancer specific outcomes.[7]

During pregnancy and in the postpartum period, iron demand often exceeds either the nutritional supply, or the capacity of the gut enterocytes to upregulate iron absorption or both.[5] Even during this high risk period, ID and IDA remain largely underdiagnosed and undertreated, resulting in potentially serious clinical consequences.[6] In addition to the usual symptoms of ID, maternal effects of ID and IDA also include an increased risk of blood transfusion, puerperal pyrexia and wound infection, heart failure and possibly risk for significant post-partum haemorrhage and death.[6] Obstetrical outcomes that may be adversely influenced include birth weight, preterm delivery rate, and perinatal death. Effects on the offspring can include detrimental cognitive and physical effects and impaired mother-child relationships.[8,9]

Burden of disease and diagnosis

A lack of epidemiological data from South Africa likely masks the gravity of the local burden of disease. Phathane et al. reported that the overall prevalence of anaemia in the South African population was 12.6%, and that ID is found in almost 80% of all anaemic patients.[10] ID was particularly high in females and

black Africans, at 56.7% and 50.7%, respectively. A study by Symington et al. who looked at maternal ID in an urban South African setting, found prevalences of anaemia, ID and IDA were 29%, 15% and 15%, respectively, showing the necessity of addressing ID in southern Africa.[11] More comprehensive and therapeutic-area specific studies are needed to assess the full extent of ID and IDA in South Africa.

Epidemiological data can assist to identify those patients most at risk for IDA who should at least be screened for anaemia with a haemoglobin test. This includes at least all pregnant women, everyone suspected to have gynaecologic cancer and women reporting significant abnormal uterine bleeding. Full investigation is also essential if more severe anaemia is suspected in patients who present with pallor, tachycardia, ankle oedema, and even heart failure.[7,12] The diagnosis of IDA requires laboratory-confirmed evidence of low Hb and microcytic red cell status or low iron stores.

General symptoms of ID and IDWA are non-specific, and diagnosis remains a challenge as there is no simple screening test for iron deficiency. The following blood tests are usually performed to assess patients in whom IDWA is suspected: complete blood count, serum iron, serum ferritin, transferrin saturation, and reticulocyte Hb content.[13,14] In these patients, assessment of anaemia alone is insufficient, and iron stores also need to be taken into consideration when developing a treatment plan as any disruption in iron intake or metabolism could result in anaemia. Anaemia is the final stage of the disease and measures should be taken to prevent progression to this stage to ensure better patient outcomes.[15]

Treatment

Treatment of ID and IDA needs to be individualised according to the cause, severity, previous treatment, co-morbidities, symptoms and laboratory-confirmed diagnosis. Importantly, the time available to correct the anaemia should also be taken into account. In many clinical situations, oral therapy remains the chosen first-line therapy for ID and IDA, but indications for the use of parenteral iron are increasing with reduced cost and improved safety and efficacy profiles.[16,17,18]

Typical clinical scenarios with an urgency to correct IDA include pre-operative and antenatal patients and women awaiting further treatment such as radiation or chemotherapy. Where there is such urgency, intolerance or failure of previous oral treatment, suspected or proven poor absorption, ongoing blood loss or very severe anaemia or iron deficiency, parenteral options are more attractive as the response to treatment is faster and not influenced by compliance or gastro-intestinal function and therefore more predictable.[19] The effect or the high dosage of iron has an additional bone marrow stimulating effect similar to erythropoietin.[20]

Newer innovative parenteral iron preparations, such as ferric carboxymaltose (FCM), have significant safety and efficacy advantages over older-generation IV therapies, oral preparations and even blood transfusions.[19,21,22] Its efficacy and safety have been established in 2nd and 3rd trimester pregnancy.[17,18] For women in later stages of pregnancy (>34 weeks of gestation), it is widely recommended internationally that IV iron be used as a first-line treatment.[16] In the postpartum period, oral iron therapy should be administered for those with mild ID.[19] For those with a more severe deficiency or anaemia, parenteral iron should be considered.[22]

The wide availability of safe intravenous iron therapy can dramatically reduce the use of allogenic blood transfusions.[21] In women's health parenteral high dose iron should typically replace blood transfusion in young patients without ongoing severe blood loss such as after early pregnancy complications, post-partum, post-operative, pre-operative and cancer patients awaiting therapy.[21,22] For many patients it will be a safer and even a more effective treatment with a better long term outcome. Moreover, one should consider the availability and scarcity of blood in South Africa. There is a blood shortage in South Africa with both the South African National Blood Services (SANBS), and the Western Cape Blood services often at critically low levels.[24] Blood should therefore be reserved for those who acutely need it for survival, as well as patients with significant bone marrow disease unable to produce haemoglobin from iron.

Conclusion

In conclusion, there are numerous health consequences for women that are iron deficient. There are many aspects to this condition, and there remains an unmet need for South African epidemiological data, and clear diagnostic and treatment protocols. More widespread availability and use of parenteral therapy hold great promise to help reduce blood transfusions and the high burden of anaemia among South African women.[25]

There is a general lack of awareness of, and a lack of attention to the prevention, short and long term management of iron deficiency among female patients in South Africa. This is despite the obvious detrimental effects on the health and well-being of the women and children of our country. Although there is a clear need to address these issues in South Africa, there is a lack of guidelines, clear recommendations and implementation thereof for the diagnosis and treatment of this condition especially for female patients.

References

1. *Lin Y-W, Wang J. Structure and function of heme proteins in non-mative states: a mini-review. J Inorg Biochem 2013:129;162-171. doi: 10.1016/j.jinorgbio.2013.07.023.*
2. *Andreini, C., Putignano, V., Rosato, A. & Banci, L. The human iron-proteome. Metallomics 10, 1223–1231 (2018).*
3. *Philpott, C. C., Ryu, M. S., Frey, A. & Patel, S. Cytosolic iron chaperones: Proteins delivering iron cofactors in the cytosol of mammalian cells. J. Biol. Chem. 292, 12764–12771 (2017).*
4. *Ginzburg, Y. Z. & Li, H. Crosstalk between iron metabolism and erythropoiesis. Adv. Hematol. 2010, (2010).*
5. *Short, Matthew and Domagalski, J. Iron Deficiency Anemia: Evaluation and Management - American Family Physician. Am. Fam. Physician 87, 98–104 (2013).*
6. *Coad, J. & Pedley, K. Iron deficiency and iron-deficiency anemia in women. Scand. J. Clin. Lab. Invest. 74, 82–89 (2014).*
7. *Mirza, F. G., Abdul-Kadir, R., Breymann, C., Fraser, I. S. & Taher, A. Impact and management of iron deficiency and iron-deficiency anemia in women's health. Expert Rev. Hematol. 11, 727–736 (2018).*
8. *Tran, T. D. et al. Impact on Infants' Cognitive Development of Antenatal Exposure to Iron Deficiency Disorder and*