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Review

Iron deficiency and sexual dysfunction in women

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Abstract

Introduction: Sexual dysfunction negatively affects approximately 40% to 50% of adult women across various stages of life. Common risk factors include sexual traumas, relationship problems, chronic conditions, medication side effects, and poor physical health, including iron deficiency.
Objectives: This review summarizes a presentation from a symposium that discussed the types and causes of sexual dysfunction at key times in women's lives, focusing on the relationship between iron deficiency and sexual dysfunction.
Methods: The symposium was held at the XV Annual European Urogynaecological Association Congress, Antibes, France, in October 2022. Symposium content was identified through literature searches of PubMed. Original research, review articles, and Cochrane analyses discussing sexual dysfunction in association with iron deficiency/anemia were included.
Results: Iron deficiency in women is commonly caused by abnormal uterine bleeding, but women may develop iron deficiency anemia (IDA) because of increased iron needs or reduced iron intake/absorption. Treatment with oral iron supplementation has been shown to improve sexual function in women with IDA. Ferrous sulphate is considered as a standard of care for oral iron treatment; prolonged-release iron formulations have improved tolerability, enabling lower doses and better tolerability.
Conclusion: IDA and sexual dysfunction are related, so the identification of sexual dysfunction or iron deficiency in a woman should prompt an investigation of the other condition. Testing for iron deficiency is an inexpensive and simple step that can be routinely included in the workup of women with sexual dysfunction. Once identified, IDA and sexual dysfunction in women should be treated and followed to optimize quality of life.

Keywords: anemia; female sexual dysfunction; iron deficiency; childbirth; dyspareunia.

Introduction

Sexual response, while fundamentally biological, is a complex phenomenon influenced by relationship and/or partner factors and the individual's psychological status (eg, body image, history of trauma, or concomitant depression), medical status, and cultural and/or religious beliefs.[1] Indeed, sex has been described as "the supreme example of a psychosomatic entity."[2] Given these complexities, it is not surprising that sexual dysfunction is common in adult women, affecting an estimated 40% to 50%,[3,4] and has a significant negative impact on quality of life (QoL).[4,5]

Sexual dysfunction is defined as a clinically significant impairment of an individual's ability to respond sexually or experience sexual pleasure, where these impairments cause the person distress.[1] Therefore, the definition of sexual dysfunction includes both reduced sexual function and sex-related distress.[6] The prevalence of sexual distress varies in the literature depending on the study and how distress is measured. For example, the age-adjusted prevalence of sexually related distress in US women was estimated to be 22% when distress was defined as a Female Sexual Distress Scale score ≥15,[7] but a 2020 community-based study in Australia reported that 50% of premenopausal women experienced sexually-related distress when the definition was a score ≥11.[8]

Women may experience sexual dysfunction at any stage during their lives, because risk factors for sexual dysfunction can occur at any age.[3] While some of these risk factors are related to past sexual trauma or current relationship problems, some women without trauma and in healthy relationships develop sexual dysfunction as a result of chronic conditions, poor physical or mental health, and/or as a side effect of medication.[3] Moreover, the risk of sexual dysfunction is higher during certain times of a woman's life, such as those after childbirth or during menopause.

Perhaps a lesser-known risk factor for sexual dysfunction in women is iron deficiency, which is more prevalent in women than men and can occur at any time in life.[9] Iron deficiency anemia (IDA) in women may originate from lack of iron intake or absorption, increased iron needs, and increased iron loss. Common reasons for female IDA are menstruation and dietary issues in children/adolescents, physiologic demands and hemodilution during pregnancy, abnormal uterine bleeding (AUB) in pre- and perimenopausal women, and nutritional deficiencies and chronic disease in older women.[9]

The reasons underlying the relationship between low iron levels and sexual dysfunction are multifactorial but include neurologic, endocrinologic, and psychological factors.[10] Moreover, IDA has many signs and symptoms that are present

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in women with sexual dysfunction, such as fatigue, anxiety, depression, and cognitive impairment.[10]

This article describes the relationship between iron deficiency and sexual dysfunction in women, focusing on the pathogenesis of iron deficiency, conditions with a high risk of iron deficiency, the potential pathogenic relationship between iron deficiency and sexual dysfunction, and the impact of iron treatment on sexual function.

Methods

The content of this article is based on a presentation at a symposium held on October 20, 2022, at the XV Annual European Urogynaecological Association Congress inAntibes, France. The speakers at the symposium (and authors of this review) conducted literature searches of PubMed for articles on sexual dysfunction in women in association with key terms for iron deficiency and anemia.

Pathogenesis of iron deficiency in women

IDA is commonly observed in women during adolescence, menstruation, physiologic demands, and hemodilution associated with pregnancy; in pre- and perimenopausal women experiencing AUB; and in older women with nutritional deficiencies and chronic disease.[9]

Most of the total iron in the body (~70%) is present within heme-containing proteins, principally hemoglobin in circulating erythrocytes and myoglobin in muscle tissue. Most of the remaining iron is stored as ferritin or hemosiderin.[11] A very small proportion of iron (<1%) is present in enzymes or bound to transferrin in plasma.[11]

Because excess iron is toxic to cells, iron homeostasis is tightly controlled to maintain levels within the normal range.[12] This system is mainly controlled by the peptide hormone hepcidin, an acute-phase reactant that is primarily synthesized in the liver.[12]

Iron deficiency is a reduction in total body iron and may occur with or without anemia, which is a reduction in the quantity of red blood cells or in their hemoglobin content, leading to microcytic and hypochromic red blood cells.[13] The World Health Organization (WHO) estimated that 29.9% of women aged 15 to 49 years had anemia in 2019,[14] and while the global prevalence is decreasing, the absolute number of women affected is increasing with worldwide population growth.[15,16]

As well as being an essential component of hemoglobin, iron is crucial for cellular functions, including energy projection, metabolism, DNA replication, and a range of functions in which iron is an enzymatic cofactor.[17] The most common signs and symptoms of iron deficiency are weakness, tiredness, difficulty concentrating, and impaired work productivity.[13] Unsurprisingly, these factors are closely linked to sexual function.

Conditions with a high risk of iron deficiency in women

The causes of IDA are multifactorial (Figure 1)[18,19] but may originate from 3 common underlying causes: lack of iron intake or absorption, increased iron needs, and increased iron loss. As stated previously, common reasons for female IDA are menstruation and dietary issues in children/adolescents, physiologic demands and hemodilution during pregnancy, AUB in pre- and perimenopausal women, and nutritional deficiencies and chronic disease in older women.[9]

Nutritional causes

Low iron intake is a common cause of iron deficiency in vegetarians, vegans, and those with eating disorders.[20-23] Endurance athletes form another category of women at risk of iron deficiency. Since many of these women have amenorrhea due to hypothalamic-pituitary-ovarian axis suppression, an increased risk of iron deficiency may seem counterintuitive.[19] However, these women may have reduced iron intake because of restrictive diets, poor iron absorption because of exercise-related inflammation, or increased iron losses in sweat or via hemolysis.[18,19]

Women with eating disorders often experience sexual dysfunction,[24,25] which is multifactorial and often related to past sexual trauma, bullying, and direct or indirect violence.[25] As a result, these women often have poor sexual self-concept, low self-esteem, anxiety, and depression.[25] Potential physiologic etiologies are less well studied in the literature, so the relationship between iron deficiency and sexual dysfunction in these women is unclear, although some data indicate that sexual dysfunction is worse in those with persistent amenorrhea.[26]

Abnormal uterine bleeding

AUB that may lead to IDA includes menorrhagia (heavy menstrual bleeding) and metrorrhagia (irregular and heavy menstrual flow), with the latter often occurring during adolescence and perimenopause. Menorrhagia, which affects about 20% to 30% of women, is the leading cause of IDA in premenopausal women,[18,27] and menorrhagia-related IDA has a marked negative effect on health-related QoL.[28] In a European survey of 330 women with menorrhagia, approximately 62% reported that their sexual life was greatly affected.[27]

All forms of AUB should be thoroughly investigated, as there are many potential underlying etiologies, both gynecologic (eg, polyps, adenomyosis, polycystic ovaries, leiomyomata, and malignancy) and hematologic (eg, coagulopathies and thrombocytopenia).[29]

In addition to being a cause of IDA, AUB has been shown to negatively affect sexual function, either directly or through effects on psychological and social functioning.[30]

Pregnancy and the postpartum period

IDA is common during pregnancy, when both iron requirements and blood volume increase, and may be associated with restless leg and pica syndromes.[31] Pregnant women need a total of 1040 mg of iron during pregnancy, including 270 mg for the fetus and 450 mg for the increased red blood cell mass.[32] Most of this iron comes from physiologic iron stores, since the typical diet contains about 10 to 20 mg/d and only 10% to 20% of dietary iron is absorbed.[33] Therefore, it is important to monitor and treat low iron levels during pregnancy because IDA is associated with increased perinatal morbidity and mortality for the mother and the neonate, with an increased risk of prematurity, preeclampsia, placental abruption, low birth weight, and peripartum blood loss, as well as impaired neonatal cognitive function.[31,34-37]

Postpartum anemia affects between 25% and 50% of women, depending on the geographic region and the definition of postpartum anemia (hemoglobin level and time after delivery).[38-40] Women with iron deficiency in the postpartum period may experience impaired cognitive

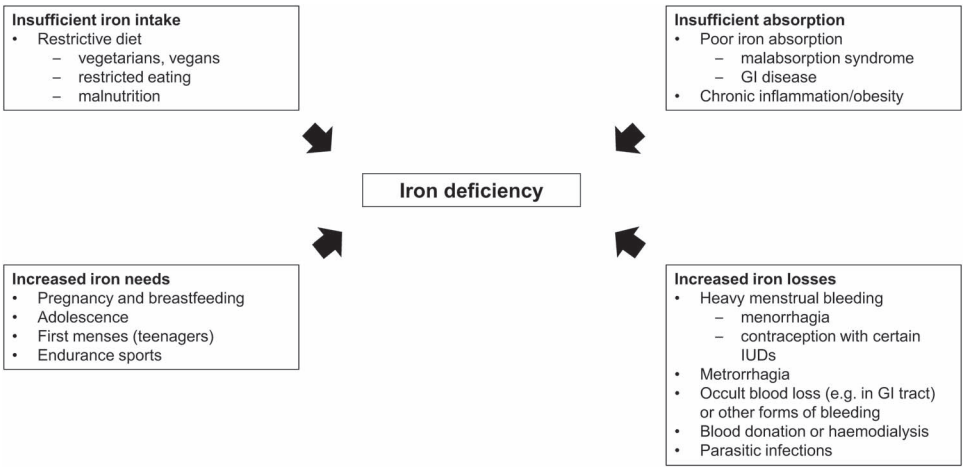

Figure 1. Common causes of iron deficiency in women.[18,19] GI, gastrointestinal; IUD, intrauterine device.

function, fatigue, and depression[41-43] and have difficulties with breastfeeding and infant-mother bonding.[44]

The presence of postpartum IDA may exacerbate existing sexual difficulties after childbirth, which are common, particularly during the first 6 months postpartum.[45] Between 41% and 83% of women experience sexual dysfunction in the first 2 to 3 months postpartum,[46-50] and up to 64% have sexual dysfunction at 6 or 12 months postpartum.[46,51] The most common form is sexual desire disorder, which accounts for 80% to 90% of sexual dysfunction after childbirth.[51,52] However, a substantial proportion of women also experience arousal problems, difficulty achieving orgasm, and pain during intercourse.[46,50,53,54] A very common form of sexual dysfunction in the postpartum period is dyspareunia, affecting about 40% to 60% of women in the first 3 months after delivery.[46,49,50] The incidence of dyspareunia is directly related to the degree of perineal trauma and may persist for longer than a few months or even >1 year in women with a history of nongenital chronic pain.[55]

Chronic disease and aging

Iron deficiency may be related to chronic disease, inflammatory states, or obesity, as a result of increased hepcidin concentrations.[18] With the growing prevalence of obesity internationally, physicians should be alert to the potential for iron deficiency in women with a high body mass index.[19] Inflammation and obesity upregulate the synthesis of hepcidin, which leads to a reduction in intestinal iron absorption and the inhibition of iron release from macrophages.[56] This results in what is known as functional iron deficiency, in which enough iron is stored in the body but insufficient iron is being mobilized to where it is needed.[18]

Data from patients with inflammatory bowel disease show that intestinal iron absorption is inhibited mainly by systemic inflammation and hepcidin production rather than by the site or type of local inflammation in the bowel.[57]

In elderly people, iron deficiency may have a number of causes, such as poor nutrition, chronic disease (eg, cancer, rheumatologic conditions, thyroid dysfunction, or chronic kidney disease), medications, and a blunted hematopoietic response.[58]

There is a paucity of research on the relationship between sexual dysfunction and iron deficiency related to chronic disease. Nevertheless, women with chronic kidney disease (a common cause of IDA) have impaired sexual function compared with women who do not.[59] Older women often experience reductions in libido, genital sensitivity, arousal, and lubrication and increased pain with sexual activity after menopause.[60-65] The extent to which these issues are exacerbated by iron deficiency is not known. However, with age, women adapt to the physical changes by altering their sexual behaviors and prioritizing different aspects of sex. As a result, low desire causes more distress in younger than older women, so as a form of sexual dysfunction, its prevalence is higher in the younger age group.[66] This highlights the need for research into what constitutes "normal" sexual function in peri- and postmenopausal women and into tools to accurately identify sexual dysfunction in this age group.

Potential pathogenic relationship between iron deficiency and sexual dysfunction

When compared with women without iron deficiency, those with iron deficiency have significantly worse general health and well-being and impaired QoL. General health and well-being are closely related to sexual health; in fact, the WHO defines sexual health as "a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity." It is therefore unsurprising that iron deficiency can negatively affect sexual function and that many of the symptoms of iron deficiency, such as fatigue, anxiety, depression, and cognitive impairment, are linked to sexual dysfunction.[10]

Several studies have demonstrated reduced sexual satisfaction and function in women with IDA. Nikzad and colleagues used the Female Sexual Function Index (FSFI) and Larsson index to assess sexual function in 129 Iranian women, 52 with IDA and 77 without.[67] They found that all domains of sexual function and sexual satisfaction were significantly lower in the women with IDA than in those without. The mean FSFI score was 26.8 in the group without IDA (meeting the threshold for normal sexual function on this scale), whereas it was 19.8 in the group with IDA ($P < .001$), indicating sexual dysfunction. This study also found a significant linear relationship between serum iron parameters (eg, hemoglobin, hematocrit, ferritin, and iron) and FSFI total score, Larsson sexual satisfaction score, and 5 FSFI domains (desire, arousal, lubrication, orgasm, and satisfaction; $P < .01$).[67]

A cross-sectional pilot study among 45 middle-aged women (mean age, 52 years) who were nonanemic investigated the relationship between iron parameters and sexual function indices.[10] Although no significant correlation was found between hemoglobin or ferritin levels and FSFI subscale scores in this study, the researchers did report that women with ferritin levels <50 μg/L were less likely to enjoy intercourse or find their partner desirable as compared with women whose ferritin levels were ≥50 μg/L.[10]

The reasons for the relationship between low iron levels and sexual dysfunction are multifactorial but include neurologic, endocrinologic, and psychological factors.[10] First, iron deficiency influences the production of dopamine and norepinephrine, which are both dependent on iron-containing tyrosine hydroxylase.[10] In animal studies, iron deficiency was associated with reduced expression of dopamine transporters and D1 and D2 receptors, increased extracellular dopamine levels,[68] and reduced uptake of dopamine in the striatum.[68-70] Dopamine is one of the key neurotransmitters involved in sexual response, with various dopaminergic cerebral pathways involved in desire, motivation, orgasm, and reward.[10,71] This suggests that reduced functionality of dopaminergic pathways caused by low iron levels may be an important biochemical component of sexual dysfunction in women.[10]

Second, iron deficiency is associated with hormonal changes that may affect sexual function. For example, levels of prolactin, a hormone associated with hypoactive sexual desire disorder, are elevated during iron deficiency, and there are changes in peripheral prolactin receptor expression.[10] Iron deficiency also reduces serum levels of T3 and T4 by inhibiting the release of thyroid-stimulating hormone from the pituitary gland, and subclinical and clinical hypothyroidism is associated with sexual dysfunction in women.[72]

Third, psychological factors, such as depression, anxiety, and dysthymia, are associated with iron deficiency and sexual dysfunction in women.[10] The relationship between depression/anxiety and sexual dysfunction is well known, and sexual dysfunction is a common comorbidity of depression in women.[73,74] In fact, sexual dysfunction may still be present long after a depressive episode has resolved. In women with anxiety, the most common form of sexual dysfunction is a loss of motivation/desire.[73,74] The impairment of sexual function in women with anxiety or depression may be exacerbated by iron deficiency, which may favor avoidance behavior, a blunted positive affect, and a lower tendency to initiate social contact and sexual activity.[10]

Impact of iron treatment on sexual function

One of the few studies to investigate the impact of iron supplementation on sexual function was conducted by Gulmez and colleagues in 207 women with IDA.[75] These women (mean age, 33.6 years) completed the Beck Anxiety Inventory (BAI), FSFI, and QoL index questionnaires before and after 3 months of treatment with oral iron supplements. Before treatment, 76% of these women met the FSFI criteria for sexual dysfunction. Oral iron supplementation led to significantly increased hematocrit, serum iron-binding capacity, and levels of hemoglobin and iron ($P < .001$). In addition, the mean FSFI total score normalized after treatment (increasing from a baseline of 24.1 to 29.8), and the proportion of women meeting the criteria for sexual dysfunction decreased to 19%. All subscales of the FSFI except pain increased significantly vs baseline ($P < .001$; Figure 2). The BAI score was significantly decreased after 3 months of iron treatment ($P < .001$), indicating a reduction in anxiety, but there was no significant change in QoL scores. The change in hemoglobin was significantly correlated with the post-treatment FSFI total score ($P = .046$) and BAI score ($P < .001$). Additionally, the post-treatment BAI score was significantly correlated with the post-treatment FSFI score ($P < .001$), suggesting that amelioration of anxiety was an important factor in improving sexual function.

Iron supplementation

Oral iron supplementation is usually the first step in the treatment of IDA[76] and has been shown to correct anemia and improve health-related QoL and sexual function in women.[28,75] Several oral iron supplements are available, differing in the dosage, salt, chemical state (as trivalent ferric ions [Fe^{3+}] or divalent ferrous ions [Fe^{2+}]), and preparation (slow release vs standard).[77] The choice of oral supplementation should take into account efficacy, tolerability, and patient adherence.[78] The most common adverse events with oral iron preparations are gastrointestinal disorders: heartburn, pain, nausea, constipation, and diarrhea.[77] The incidence of adverse events appears to be dose related,[77] but prolonged-release formulations of ferrous iron, which limit the iron bolus load in the gastrointestinal tract, are better tolerated than the standard preparations.[79] The WHO recommendations for anemia treatment note the importance of choosing a slow-release preparation to improve iron absorption and tolerability and therefore maximize adherence while using a lower dose of iron.[78]

Ferric iron preparations are better tolerated than standard preparations of ferrous iron but are poorly absorbed, with bioavailability that is 3 to 4 times lower than that of ferrous iron.[77,78] As a result, the most commonly used iron preparations include ferrous salts, such as fumarate, gluconate, sulphate, or glycine sulphate.[77,78] Of these, ferrous sulphate is the most widely studied[80] and considered the standard of care for oral iron supplementation based on its efficacy/safety profile and cost.[77] Ferrous sulphate is the only oral iron preparation in the WHO's list of essential medicines.[81]

Conclusion

Women may experience sexual dysfunction at any time during their lives, but iron deficiency can increase the risk of, or exacerbate, sexual dysfunction in all age groups. Because IDA and sexual dysfunction are related, the identification of sexual dysfunction or iron deficiency in a woman should prompt an investigation of the other condition.[10,67] Testing for iron deficiency is an inexpensive and simple step that can be routinely included in the workup of women with sexual dysfunction.[82] Particular attention should be paid to iron status in pregnant, obese, or older women; those with AUB, chronic disease, or restrictive diets; and endurance athletes.[13,18,19] When iron deficiency is present, patients should be offered individualized treatment to restore iron status and optimize QoL outcomes,[28] including an improvement in sexual function.[75]

Further research is needed to clarify the pathogenic role of iron deficiency in women with restrictive diets and chronic disease and to establish the "norms" of sexual function in older women.

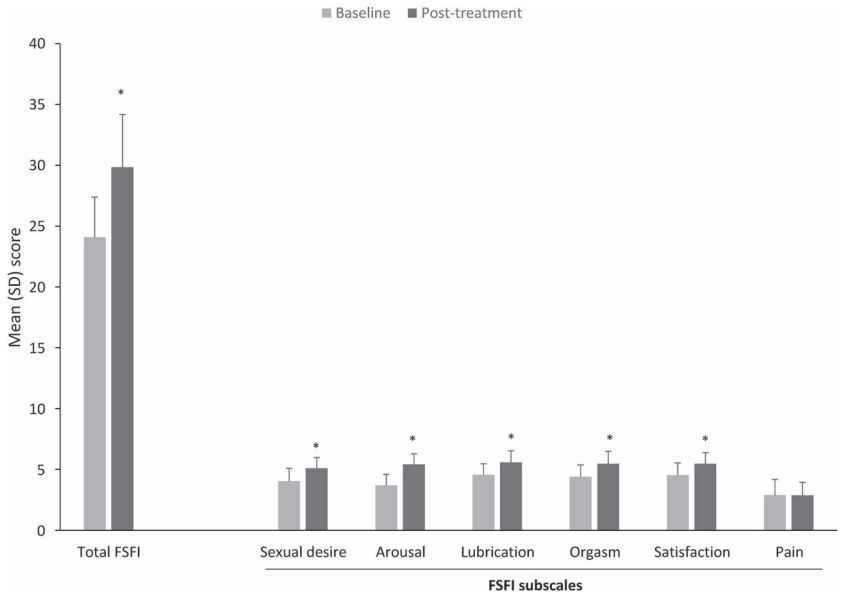

Figure 2. The effect of 3 months of oral iron treatment on sexual function, measured with the FSFI in women with iron deficiency anemia (n = 207).[75] *$P < .001$ vs baseline. FSFI, Female Sexual Function Index.

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Author contributions

Conception and design: M.S., M.E.-P., A.M.-P., A.P. Acquisition of data: M.S., M.E.-P., A.P. Analysis and interpretation of data: M.S., M.E.-P., A.P. Drafting of article: A.M.-P. Critical revision of drafts for intellectual content: M.S., M.E.-P., A.M.-P., A.P. Final approval of version to be published: M.S., M.E.-P., A.M.-P., A.P.

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Conflicts of interest: M.S. has been a speaker for Pierre Fabre, Coloplast, and Laborie. M.E.-P. has been a speaker for Pierre Fabre. A.M.-P. is an employee of Pierre Fabre. A.P. has been a speaker for Pierre Fabre and receives royalties from Springer Publishers.

Data availability

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

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