Impact of levonorgestrel-releasing intrauterine system on levels of serum hemoglobin and ferritin in women with a normal and elevated body mass: 1-year follow-up

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ABSTRACT

Objective: To explore the relationship between overweight and iron status and identify the prevalence and nature of iron deficiency (ID) in a cohort of young healthy overweight and normal weight women using the levonorgestrel-releasing intrauterine system (LNG IUS) as a contraceptive method.

Design: Prospective non-randomized open-label trial.

Sample: 33 women who wanted to use the LNG IUS for contraception.

Methods: The participants were divided into 2 groups according to their body mass index (BMI) at the beginning of the research: 19 women formed the LNG-IUS I group (BMI ≤25); 14 women were included in the LNG-IUS II group (BMI≥25). The women were also analyzed according to levels of serum hemoglobin: >120 g/L (non-anemic) and <120 g/L (anemic) and serum ferritin: <15ng/mL (iron deficiency) and >15 ng/mL.

Results: At the beginning of the research, 12 women (22.2%) were diagnosed with anemia and 15 women (27.8%) with severe iron deficiency (<15 ng/mL). After six months of using the contraception, statistically significant increases in S-Hb were found in both S-Hb <120 subgroups (+20.2; p=0.01 and +21.1; p< 0.05 g/L), respectively. Instead, S-Fe increased in the LNG-IUS I group (+17.58; p=0.01 ng/L) but decreased in the LNG-IUS II group (-8.45; p=0.50 ng/L).

After 12 months' use of the contraceptive method, S-Fe increased by +11.00; p=0.11 ng/mL in the LNG-IUS I group, but decreased by -1.07; p=0.3 ng/mL in the LNG-IUS II group.

Conclusions: There are various possible reasons for iron deficiency anemia among women with different BMIs, and it cannot be explained only by menstrual bleeding patterns. Our study shows that, among women who chose the LNG IUS for contraception, serum hemoglobin and ferritin levels increased faster in the group with a normal body mass than in the group with elevated body mass.

KEYWORDS

Levonorgestrel-releasing intrauterine system, serum hemoglobin, serum ferritin, contraception, anemia, iron deficiency.

Introduction

The levonorgestrel-releasing intrauterine system (LNG IUS) has been used for contraception in Europe since 1990 [1]. The LNG IUS also significantly reduces menstrual bleeding [3], which is particularly important for women with menorrhagia – pathological blood loss during the menstrual period (over 80 ml). In these cases, the LNG IUS normalizes menstrual bleeding [3-5], thus restoring the iron reserves in the body and the level of serum hemoglobin (S-Hb) [5].

The LNG-IUS has been assessed for its effect on menstrual blood loss and can work as an alternative to hysterectomy [3,6-10]. Menstrual blood loss with the LNG-IUS dropped by 86% at 3 months, and 97% at 6 months. It was observed that parameters of anemia, such as hematocrit and ferritin levels, improved [9].

Globally, the two most widespread nutritional disorders are obesity and iron deficiency (ID). ID and ID anemia (IDA) are major public health issues [10]; both are more observed in developing countires, although decreased iron levels are also found in developed countries. Epidemiological evaluation shows that anemia is more frequent with age [11]. Previous studies show a link between ID and obesity in children and adults [12,13]. A decreased level of serum iron was found with weight gain and increased body mass index (BMI).

Worldwide, reproductive age women face a risk of IDA, which causes morbidity and mortality [14]. This could be connected with higher parity, which reduces iron levels in these women [15].

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Abbreviations
LNG IUS: Levonorgestrel-releasing intrauterine system; **S-Hb:** Serum hemoglobin; **S-Fe:** Serum ferritin; **ID:** Iron deficiency; **IDA:** Iron deficiency anemia

There is a tendency for elevated hemoglobin and ferritin concentrations in obese populations. Previous studies have identified a link between ID and obesity [15].

Although many studies have evaluated the impact of the LNG IUS on anemia indicators, these studies offer only limited insight into changes in anemia indicators in relation to BMI. Our study aimed to identify the correlation between overweight and iron status, and to determine the prevalence and nature of ID in a cohort of young healthy overweight and normal weight women using the LNG-IUS as a method of contraception.

Materials and Methods

Women aged 18-45 years attending I. Vasaraudze's Private Clinic Ltd. from 1 January 2012 to 31 December 2013 to be counseled on contraception were invited to participate in a prospective non-randomized open-label research study. The women themselves chose a contraceptive method, and the ones who chose the LNG-IUS were included in the study. They were divided into two groups: LNG-IUS with BMI ≤ 25 (LNG-IUS I group) and LNG-IUS with BMI ≥ 25 (LNG-IUS II group).

According to their S-Hb and serum ferritin (S-Fe) levels at the start of the study, the women were further divided into 4 subgroups: S-Hb < 120 and ≥ 120 g/L; S-Fe < 15 and S-Fe ≥ 15 ng/mL. When choosing the contraceptive method, the respective contraindications were considered. The goal was to recruit at least ten women in each group, or as many women as possible until the end of the recruitment phase.

Women who met the criteria gave their informed consent before they were included in the sample; the women started to use the hormonal contraception method in accordance with the instructions of the manufacturer. When starting the study, all women were measured, without footwear, for body mass and height. Height was approximated to the nearest 0.1 cm, and weight was approximated to the nearest 0.1 kg.

They were examined at the beginning of the study, after six months and after twelve months. Blood samples for testing were collected a fasting period of 8–12 hours via venipuncture.

Statistical analysis

The IBM SPSS v.23. program was used. Data were presented as mean values and standard deviation (mean ± SD) for continuous variables, and as counts and percentages [%] for categorical variables. Comparisons were made using an independent samples t-test. Cohen's d was used to calculate the effect size (>0.8 = large, 0.8–0.3 = medium, and <0.3 = small). The relationships between variables were evaluated using the Spearman-Rank correlation coefficient (rs). All tests were considered statistically significant at $p<0.05$.

As no statistical differences between indicators were observed based on p values, Cohen's d values were calculated to evaluate effect sizes. However, a big statistical effect does not always mean a big clinical difference between indicators.

The research had been approved by the Riga Stradins University ethics committee on 26 September 2013.

Results

454 women who attended the clinic from 1 January 2012 to 31 December 2013 were invited to participate in the research. Of these, 141 (31.1%) agreed and underwent the examinations necessary to be included in the research; 33 women (23.4%) underwent all the necessary examinations and met the inclusion criteria. After being included, the women were divided into two groups according to their BMI at the beginning of the research: 19 women (57.6%) were included in the LNG-IUS I group; and 14 (42.4%) in the LNG-IUS II group. During the research, 2 women (6.0%) were excluded from the study groups because they had side effects and stopped using the contraception. The baseline characteristics of the study groups are summarized in Table 1.

At the beginning of the research, the average level of S-Hb in the LNG-IUS I group was 126.15±9.7 g/L, versus 126.8±12.78 g/L in the LNG-IUS II group, without a statistically significant difference between the groups (p=0.56); after the women had been using the LNG-IUS for 6 months, S-Hb was 133.95±9.28 g/L in the first group and 132.43±9.66 g/L in the second group (p=0.64); after they had been using it for 12 months, the levels were 132.16±8.91 and 134.71±71 g/L (p=0.5), respectively (Fig. 1). After 6 months of LNG-IUS use, S-Hb reached its plateau in the first group, whereas in the second group it continued to increase beyond 6 months, as shown

Table 1 Baseline characteristics of women who participated in the study (N=33)

	LNG-IUS I (N=19)	LNG-IUS II (N=14)	p-value	Cohen's d
Age (years)	33.95±6.15 (23-44)	36.21±4.44 (29-44)	0.25	0.43
BMI (kg/m²)	22.10±2.14 (18.00-24.90)	28.00±2.85 (25.3-35.6)	**<0.001**	**2.38**
Deliveries	1.74±0.56 (0-3)	1.50±1.09 (0-3)	0.42	0.27

Figure 1 Average serum hemoglobin levels (g/L) in the research groups

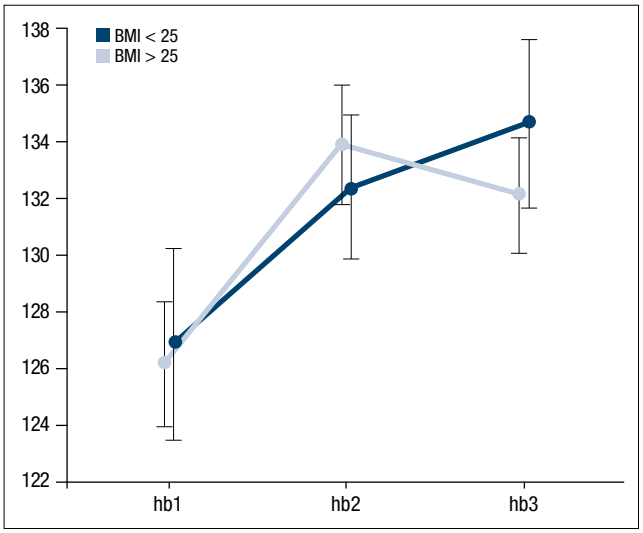

Table 2 Levels of serum hemoglobin (g/L) and serum ferritin (S-Fe) in the research groups according to baseline levels of serum hemoglobin

Group	Parameter		Baseline	6 months	12 months
LNG- IUS I	S-Hb (g/L)	S-Hb<120	113.00±5.52 (107-119)	133.20±11.10 (119-147)	127.60±9.90 (115-141)
		S-Hb≥120	130.85±5.51 (122-137)	134.21±9.00 (122-151)	133.78±8.27 (116-148)
		p-value	**<0.001**	0.84	0.20
		Cohen's d	**3.10**	0.10	0.66
	S-Fe (ng/mL)	S-Hb<120	11.06±5.44 (5.40-19.00)	28.64±21.30 (11.30-63.10)	39.64±15.07 (24.70-61.20)
		S-Hb≥120	42.54±24.51 (8.40-90.50)	48.72±18.45 (8.40-73.20)	50.45±25.48 (8.40-96.10)
		p-value	0.01	0.04	0.39
		Cohen's d	**1.77**	**1.00**	0.52
LNG- IUS II	S-Hb (g/L)	S-Hb<120	113.00±8.83 (100.00-119.00)	134.00±12.93 (124-153)	132.00±15.12 (117-153)
		S-Hb≥120	132.40±9.51 (123-149)	131.80±8.80 (120-150)	135.80±10.04 (125-152)
		p-value	**0.004**	0.71	0.58
		Cohen's d	**2.11**	0.18	0.23
	S-Fe (ng/mL)	S-Hb<120	24.57±25.36 (2.40-54.70)	16.12±14.52 (2.4-35.20)	15.05±13.05 (2.40-31.50)
		S-Hb≥120	35.17±26.03 (8.90-89.80)	47.11±37.11 (22.20-132.00)	49.01±31.48 (10.60-102.00)
		p-value	0.50	0.04	0.01
		Cohen's d	0.41	**1.10**	**1.43**

by the level after 12 months of use. Tables 2 and 3 summarize the S-Hb and S-Fe levels recorded in the study groups divided according to different baseline levels of S-Hb (Table 2) and S-Fe (Table 3). At the beginning of the research, the average level of S-Fe was 34.25±24.94 ng/mL in the LNG-IUS I group and 32.14±25.34 ng/mL in the LNG-IUS II group, with no statistically significant difference between the groups (p=0.98). After 6 months, the average level of S-Fe was 43.44±20.71 in group I and 38.26±34.84 in group II (p=0.91). After 12 months, the average level of S-Fe was 47.61 ± 23.31 in group I and 39.31± 31.29 in group II (p=0.3) (Fig.2). S-Fe did not reach its plateau level in either of the groups and continued to increase also after 12 months of use.

In the LNG-IUS II, S-Hb<120 subgroup, S-Fe level decreased from 24.57±25.36 ng/mL to 16.12±14.52 after six months' use of the contraception; after 12 months, it was found to have decreased further, to 15.05±13.05 ng/mL (Table 2).

After exploring the possibility of correlations between BMI, age, S-Hb and S-Fe, it was found that there was no statically significant correlation (p>0.05).

Figure 2 The average level of serum ferritin ng/mL in the research groups

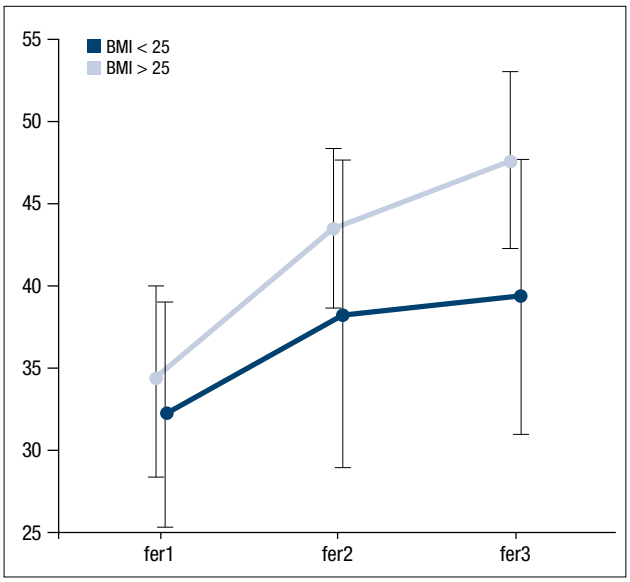

Table 3 Levels of serum hemoglobin (g/L) and serum ferritin (ng/mL) in the research groups divided according to baseline ferritin levels

Group	Parameter		Baseline	6 months	12 months
LNG- IUS I	S-Hb (g/L)	S-Fe<15	116.16±8.23 (107-126)	137.16±7.65 (127-147)	131.00±9.12 (115-141)
		S-Fe≥15	130.77±6.31 (119-137)	132.46±9.86 (119-151)	132.70±9.14 (116-148)
		p-value	**<0.001**	0.31	0.71
		Cohen's d	**1.97**	0.53	0.11
	S-Fe (ng/mL)	S-Fe<15	16.83±19.54 (5.40-56.30)	31.60±21.75 (8.40-63.10)	35.00±18.74 (8.40-61.20)
		S-Fe≥15	42.30±24.16 (17.90-90.50)	48.90±18.54 (12.20-73.20)	53.42±23.51 (17.90-96.10)
		p-value	0.03	0.09	0.11
		Cohen's d	**1.16**	**0.8**	**0.86**
LNG- IUS II	S-Hb (g/L)	S-Fe<15	119.75±15.67 (100-138)	126.75±4.57 (120-130)	127.75±2.06 (125-130)
		S-Fe≥15	129.70±11.07 (115-149)	134.70±10.38 (124-153)	137.50±12.25 (117-153)
		p-value	0.20	0.17	0.03
		Cohen's d	**0.91**	**1.00**	**1.12**
	S-Fe (ng/mL)	S-Fe<15	7.25±4.62 (2.40-12.90)	16.77±13.71 (2.40-28.60)	25.32±25.24 (2.40-56.10)
		S-Fe≥15	42.10±23.13 (11.40-89.80)	46.85±37.45 (19.20-132.00)	44.90±32.86 (10.60-102.00)
		p-value	0.01	0.04	0.30
		Cohen's d	**2.10**	**1.08**	0.70

Discussion

As excessive menstrual bleeding is the most frequent cause of anemia in women of reproductive age, the considerable reduction in the menstrual bleeding that is observed in LNG-IUS users naturally leads to a long-term increase in their levels of S-Hb and S-Fe [16]. ID in the absence of anemia adversely affects physical performance, mental health and cognitive function [17].

The results of our study show that moderate ID with reduced S-Fe level for women with elevated BMI is the most common iron-related abnormality (27.8%). During the use of the contraception, a significant increase in the level of S-Hb was observed in the group of women with a normal BMI; by contrast, in the group of women with elevated BMI, significant changes were observed only after 12 months. This indicates a very gradual correction of ID. Despite this, even after using the LNG-IUS for 12 months, 21.4% of women with increased BMI had ID. Our research shows that the treatment of IDA and ID may require a longer time than that required for the correction of menstrual bleeding patterns.

Obesity is a worldwide pandemic, while ID is the most widespread single microelement deficiency.

Estrogen is important for regulating iron metabolism, cardiovascular circulatory system, skeletal muscle system, central nervous system, bacterial infections, and estrogen-related diseases [18]. Premenopausal obese and overweight women had significantly lower estradiol levels, independently of age, race and smoking habits [19].

In the female body, serum iron storage is closely linked to estrogen level. A study by Qian et al. showed that estrogen is involved in regulating ferroportin expression [20]. Ferroportin and hepcidin are critical proteins for the regulation of systemic iron homeostasis. They found that transcription of hepcidin was reduced by estrodiol treatment. In young women, hepcidin inhibitionby high estrogen increases iron uptake, in order to compensate for iron loss during menstruation. This mechanism also plays a role in increased iron reserves in young women who use oral contraceptives. These authors' results show that estrogen deficiency could not lead to iron increase. Previous studies have shown evidence of regulatory effects of estrogen

on iron metabolism, but future studies are still necessary to clarify, in detail, the mechanisms involved.

Many studies [21-25] show that iron plays a role in pathogenesis of many diseases, such as ischemic heart disease, cancer, diabetes, infections and neurodegenerative disorders. Healthy levels of iron have not yet been standardized, but it is likely that ID or iron overload could cause adverse health effects. Jian et al. [20] reported that ID in young women contributes to high breast cancer recurrence, while increased iron plays a role in high breast cancer incidence in postmenopausal women.

It has been shown in the literature that elevated c-reactive protein and low median hepcidin can detect a greater percentage of participants with ID [26]. Previous studies did not establish a relationship between BMI and Fe status. Obese women had lower Fe absorption when compared with overweight women. This may be due to subclinical inflammation associated with obesity. Previous studies have concluded that obesity is significantly related to ID [27].

Mean and median hemoglobin levels have been found to be significantly higher in abdominally obese compared with totally obese women. The mean hemoglobin level was positively and significantly associated with waist circumference and negatively and insignificantly associated with BMI. Overweight women reported greater ID than normal weight women. These findings show that overweight females are at greater risk of ID and that inflammation caused by excess adipose tissue plays a role in this phenomenon [25,26].

On the other hand, previous studies [28-35] also show higher hemoglobin and ferritin concentrations and lower transferrin saturation in overweight women. Thus, future studies involving inflammatory cytokines, soluble transferrin receptors and hepcidin are necessary to confirm the impact of obesity on iron metabolism.

Serum ferritin, which is a marker of iron metabolism, is considered a biomarker of chronic low-grade inflammation. After menopause, there are significant increases in insulin resistance (IR) and metabolic syndrome (MetS), which are very often considered inflammatory conditions. Serum ferritin levels were positively and independently associated with IR and MetS in postmenopausal women. S-Fe levels in postmenopausal women could help to identify the presence of IR and MetS [30].

However, there have been studies showing that obese and normal weight persons do not differ in total daily iron consumption. At the same time, the fat mass is regarded as a major negative predictor of serum iron level. Furthermore, a connection is reported between increased BMI and Hb, as well as high S-Fe levels [31].

A number of age-related, dietary and inflammatory-associated factors influence iron levels in overweight young women. ID and IDA could lead to exhaustion, thus reducing physical activity and further contributing to weight gain. ID and obesity are not just two prevalent conditions but are also molecularly linked and mutually affect each other [32].

Our results show that ID, as reflected by low ferritin, is still the major iron-related abnormality among overweight women. Our study also emphasizes the importance of taking into account simple ID in healthy overweight young women using LNG-IUS for contraception.

Conclusions

There are various possible reasons for IDA among women with different BMIs, and it cannot be explained only by menstrual bleeding patterns. Among women who chose the LNG-IUS for contraception, we found that S-Hb and S-Fe levels increased faster in those with a normal BMI compared with the group of women with elevated body mass.

This research shows that even women without menstrual bleeding complaints should be evaluated and, if necessary, appropriately treated for IDA before starting contraceptive use of the LNG-IUS.

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