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Effects of anemia and iron deficiency on quality of life in women with heavy menstrual bleeding

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Key words
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Conflict of interests
Pirkko Peurapää has given a lecture in the meeting sponsored by Vifor Pharma. Ian Fraser has undertaken lectures and consultancies, and received research grants from Bayer Healthcare, Merck/MSD and Vifor Pharma. Ritva Hurskainen has received grants from Helsinki University Hospital Research Funds and Academy of Finland and lecture and consultant sponsorship from Bayer Healthcare, Johnsson et Johnsson and Vifor Pharma. Jorma Paavonen has received research grants from the Academy of Finland.

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Abstract

Objective. To assess the impact of anemia and iron deficiency on health-related quality of life (HRQoL) in women treated for heavy menstrual bleeding (HMB). *Design.* Secondary analysis of a randomized controlled trial. *Setting.* Five university hospitals in Finland. *Sample.* A total of 236 women referred for HMB. *Methods.* Women were randomized to treatment with hysterectomy or a levonorgestrel-releasing intrauterine system. We defined groups based on women's pretreatment hemoglobin [hemoglobin <120 g/L (anemic) vs. hemoglobin ≥120 g/L (nonanemic)] and serum ferritin (ferritin <15 μg/L vs. ≥15 μg/L) concentrations. HRQoL was compared between groups at baseline, 6 and 12 months after treatment. Hemoglobin and ferritin were followed for 5 years. *Main outcome measures.* HRQoL was measured by the RAND 36-item health survey (RAND-36), 5-Dimensional EuroQol and two questionnaires of mental wellbeing. *Results.* At baseline, 63 women (27%) were anemic and 140 (60%) were severely iron deficient (ferritin <15 μg/L). Only 8% of the anemic women had taken iron supplementation. Twelve months after treatment hemoglobin had increased in both hemoglobin groups, but was still significantly lower ($p < 0.001$) in initially anemic women (128 g/L) compared with nonanemic women (136 g/L). Twelve months after treatment three domain scores of RAND-36 increased more (energy, $p = 0.002$; physical functioning, $p = 0.04$; social functioning, $p = 0.05$), and anxiety ($p = 0.02$) and depression scores ($p = 0.002$) decreased more in anemic compared with nonanemic women. Serum ferritin took 5 years to reach normal levels. *Conclusions.* Improved HRQoL after treatment of HMB is associated with correction of anemia. Clinicians should actively screen for anemia in women with HMB and emphasize early iron substitution as an integral part of treatment.

Abbreviations: HMB, heavy menstrual bleeding; HRQoL, health-related quality of life; LNG-IUS, levonorgestrel-releasing intrauterine system; RAND-36, RAND 36-item health survey.

Key Message

Diagnosis and treatment of anemia are important to improve quality of life among women with heavy menstrual bleeding.

Introduction

Heavy menstrual bleeding (HMB) is a common problem among women of reproductive age (1,2) and has a major impact on a woman's quality of life, disturbing physical activity and work performance as well as social and emotional life (3–6).

Heavy menstrual bleeding is a common cause of iron deficiency and iron deficiency anemia (7). Monthly menstrual iron losses without adequate dietary iron supplementation gradually reduce the body's iron stores, causing iron deficiency detected by low serum ferritin measurement (8). When the iron stores are depleted, hemoglobin production is affected and iron deficiency anemia develops (8). Recently, interest has focused on possible adverse effects of iron deficiency and iron deficiency anemia on women's health in a wider aspect. Several studies have reported reduction not only in physical performance, but also in cognitive function, mood and health-related quality of life (HRQoL) among iron-deficient, fertile-aged women (9–15).

It is not clear to what extent the decline in the HRQoL of women with HMB is caused by iron deficiency and anemia and to what extent it is related to other problems connected with heavy bleeding. It is not known either how much the improvement of HRQoL after treatment of HMB is a direct result of the correction of iron deficiency and anemia.

The aim of this study was to investigate the effects of anemia and iron deficiency on HRQoL among women with HMB and to evaluate the effects of the treatment of HMB on hemoglobin and serum ferritin concentrations and HRQoL.

Material and methods

The present study is a secondary analysis of a prospective, randomized study comparing hysterectomy and levonorgestrel-releasing intrauterine system (LNG-IUS) for the treatment of HMB. A detailed description of the original study protocol has been reported elsewhere (4,16). Briefly, the study population consisted of 236 women, who were referred for HMB to one of the five university hospitals in Finland between November 1994 and November 1997 and were randomly assigned to treatment with hysterectomy (n = 117) or LNG-IUS (n = 119). Women were 35–49 years of age, were menstruating, had completed their family and were eligible for both treatment options at baseline. LNG-IUS (Mirena; Bayer Schering Pharma Oy, Turku, Finland) was inserted during the randomization visit. The follow-up visits took place 6 and 12 months after hysterectomy or insertion of LNG-IUS and again 5 years after randomization. The participants completed questionnaires containing HRQoL instruments before randomization and before each follow-up visit. Iron substitution was allowed during the study. All women participating in the study gave written informed consent. The study was approved by the Ethics Committees of all university hospitals and by the National Research and Development Centre for Welfare and Health in Finland. This study met all the criteria for a large, effective modern study of management of HMB (17). Trial Registration: clinicaltrials.gov Identifier: NCT00966264.

The HRQoL was measured using the RAND 36-item health survey (RAND-36) (18), which includes eight dimensions: general health, physical functioning, emotional wellbeing, social functioning, energy, pain and physical and emotional role functioning. The Five-Dimensional EuroQol (19) was also used to measure HRQoL. The general health assessment was recorded on a visual analogue scale. Anxiety was measured by Spielberger 20-item state anxiety scale (20) and depression was measured with Beck's depression inventory (21).

Hemoglobin concentrations were measured at baseline, 12 months and 5 years after treatment. Ferritin concentrations and menstrual blood loss [alkaline hematin method (22)] were measured before randomization, 6 and 12 months and 5 years after treatment. Blood samples for hemoglobin and serum ferritin measurements were taken during days 1–7 of the menstrual cycle. Anemia was defined as hemoglobin <120 g/L and severe iron deficiency as serum ferritin <15 μg/L. Study groups were defined based on pretreatment hemoglobin and serum ferritin measurements as follows: (i) hemoglobin <120 g/L (anemic) and hemoglobin ≥120 g/L (nonanemic) and (ii) ferritin <15 μg/L (severely iron deficient) and ferritin ≥15 μg/L (mildly iron deficient or iron sufficient).

The two groups of primary interest were anemic vs. nonanemic women but an independent assessment with dichotomization by ferritin levels was also undertaken. We compared HRQoL, anxiety and depression scores between groups from baseline up to 12 months after treatment. Hemoglobin and serum ferritin concentrations were compared between anemic and nonanemic groups for 5 years.

Statistical analyses

All analyses were performed using the statistical software SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Student's t-test for independent samples was used to test differences in quality of life scores and hematological parameters between groups at baseline and changes between the groups after the treatment. The Pearson's correlation was used to study the correlation between hemoglobin, ferritin and menstrual blood loss at baseline. A multivariate linear regression model was used to test the association between HRQoL, anxiety and depression score changes and explaining factors (pretreatment hemoglobin, serum ferritin and menstrual blood loss). Values of $p \leq 0.05$ were considered significant.

Results

Of the 236 participants, 223 attended the 6-month follow-up visit, 228 the 12-month visit and 229 the 5-year visit. The mean age of participants was 43 years (SD 3.4) at baseline and 48 years (SD 3.3) at the 5-year visit. Data concerning baseline hemoglobin were available from 234 and baseline serum ferritin from 233 participants. Mean baseline hemoglobin of the whole study population was 125 g/L (range 88–159 g/L) and mean serum ferritin 16.1 μg/L (range 2.0–155.0 μg/L). Sixty-three women (27%) were anemic with mean hemoglobin 110 g/L (range 88–119 g/L) and mean serum ferritin 8.2 μg/L (range 2.0–34.0 μg/L). The nonanemic group (171 women, 73%) had mean hemoglobin 131 g/L (120–159 g/L) and mean serum ferritin 19.0 μg/L (2.4–155.0 μg/L). Iron deficiency was common, 140 women (60%) were severely iron-deficient determined by serum ferritin <15 μg/L. Iron sufficiency was rare in the study population. Only six women had serum ferritin over 50 μg/L, 14 women had serum ferritin over 40 μg/L and 23 women over 30 μg/L.

Table 1. Baseline characteristics of participants.

	Hb < 120 g/L n = 63	Hb ≥ 120 g/L n = 171	p value
Age (years)	43.2 (3.4)	43.0 (3.3)	NS
Parity	2.1 (1.1)	2.0 (1.1)	NS
Smoker	16 (25%)	53 (31%)	NS
Chronic illness[a]	20 (32%)	69 (40%)	NS
Iron supplementation	5 (7.9%)	10 (5.8%)	NS
Menstrual blood loss (ml)	190.1 (150.2)	105.6 (92.1)	<0.001

Data are means (SD) or number of women.
NS, not significant.
[a]The most common chronic illnesses reported were chronic back pain, hypertension and thyroid disease.

Mean menstrual blood loss was 128 mL (SD 117, range 9–742 mL). There was a significant difference in menstrual blood loss between anemic and nonanemic women (mean 190 mL, range 14–742 mL vs. mean 106 mL, range 9–707 ml, $p < 0.001$). There was a strong negative correlation between hemoglobin and menstrual blood loss ($p < 0.001$) and between ferritin and menstrual blood loss ($p = 0.001$) at baseline. Baseline characteristics of the anemic and nonanemic women are given in Table 1. It is noteworthy that only 15 of the whole study population (6%) and only five of the 63 anemic women (8%) had taken iron supplementation. One woman reported oral iron usage at 6 month's control visit and two women at the 12 month's control visit.

Mean hemoglobin increased during the 12 months after treatment of HMB from 110 g/L to 128 g/L in anemic women and from 131 g/L to 136 g/L in women with normal pretreatment hemoglobin (Table 2). After 5 years there was no longer a difference in hemoglobin concentrations (136 g/L in both groups). Serum ferritin increased in both groups after treatment of HMB. Six months after treatment ferritin was still lower in the anemic group compared with the nonanemic group (18.0 μg/L vs. 28.6 μg/L, $p = 0.002$), but there were no significant differences in ferritin concentrations between the groups 12 months after the of treatment (32.7 μg/L vs. 38.8 μg/L, $p = 0.4$). After 5 years ferritin values were still increasing, but were lower among the initially anemic group compared with the initially nonanemic group (49.3 μg/L vs. 67.5 μg/L, $p = 0.03$).

When comparing different therapies (LNG-IUS vs. hysterectomy) no significant differences in hemoglobin

Table 2. Hemoglobin and serum ferritin before and after treatment of heavy menstrual bleeding in different pretreatment hemoglobin groups.

	Baseline	6 months	12 months	5 years
Hemoglobin g/L				
Hb < 120 g/L group	110 (88–119)	[a]	128 (96–148)	136 (117–177)
Hb ≥ 120 g/L group	131 (120–159)	[a]	136 (110–157)	136 (114–156)
p value	<0.001		<0.001	NS
Ferritin μg/L				
Hb < 120 g/L group	8.2 (2–34)	18.0 (4–51)	32.7 (5–93)	49.3 (7–237)
Hb ≥ 120 g/L group	19.0 (2–155)	28.6 (3–233)	38.8 (7–258)	67.5 (5–464)
p value	<0.001	0.002	NS	0.03

Data are means (range).
NS, not significant.
[a]Hemoglobin values not available.

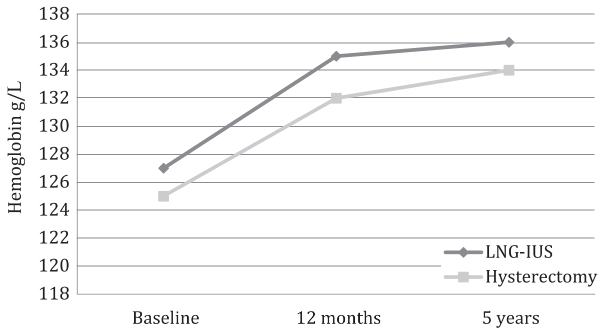

Figure 1. Blood hemoglobin concentrations among women treated with levonorgestrel-releasing intrauterine system (LNG-IUS) or hysterectomy during 5 years of follow up.

concentrations were noticed at baseline, 1 or 5 years after treatment (Figure 1).

There were no differences in the baseline RAND-36 scores for HRQoL between anemic and nonanemic groups (Table 3). Six months after treatment RAND-36 scores improved in both groups and most of the dimension scores improved more in the anemic group, but no significant differences between groups were noted. However, 12 months after treatment every dimension score of RAND-36 increased more in the anemic group compared with the nonanemic group and the differences were statistically significant in energy ($p = 0.002$), physical functioning ($p = 0.04$) and social functioning ($p = 0.05$). The five-dimensional EuroQol and visual analogue scale scores increased in both groups 6 and 12 months after the treatment, but no differences between anemic and nonanemic groups were found. No significant differences in anxiety or depression scores were found between groups before treatment or 6 months later, but 12 months after treatment anxiety ($p = 0.02$) and depression scores ($p = 0.002$) decreased more among women who were anemic before treatment, compared with women with normal pretreatment hemoglobin.

There were no differences in any HRQoL measurements between the two ferritin groups (ferritin ≥15 μg/L vs. ferritin <15 μg/L) at baseline or after treatment (data not shown).

The multivariate model showed no correlations at all between baseline menstrual blood loss and HRQoL score change 6 or 12 months after treatment (Table 4). Hemoglobin, however, was correlated with HRQoL changes. After 12 months, analysis showed a significant negative association between baseline hemoglobin and score change in most dimensions of RAND-36, indicating a better post-treatment HRQoL with lower baseline hemoglobin. A positive association between baseline

Table 3. Mean outcome scores at baseline and score change 6 and 12 months after treatment: comparison between anemic and nonanemic groups.

	Baseline			Change at 6 months			Change at 12 months		
	Hb < 120 g/L	Hb ≥ 120 g/L	p value[a]	Hb < 120 g/L	Hb ≥ 120 g/L	p value[b]	Hb < 120 g/L	Hb ≥ 120 g/L	p value[b]
Rand-36									
General health	67	63	NS	5.4	5.1	NS	6.2	5.9	NS
Physical functioning	84	83	NS	9.1	5.7	NS	9.9	4.6	0.04
Emotional well-being	67	68	NS	7.0	5.8	NS	11.7	7.1	NS
Social functioning	74	73	NS	10.6	10.1	NS	17.1	10.4	0.05
Energy	53	57	NS	12.4	8.0	NS	18.9	8.8	0.002
Pain	66	61	NS	15.2	15.2	NS	16.9	16.5	NS
Role functioning physical	67	64	NS	18.9	14.6	NS	23.6	16.4	NS
Role functioning mental	62	65	NS	20.8	15.0	NS	25.8	14.6	NS
EQ-5D	0.76	0.77	NS	0.11	0.08	NS	0.09	0.10	NS
VAS	89	90	NS	5.6	5.4	NS	6.9	4.4	NS
Anxiety	32	32	NS	−1.7	0.01	NS	−4.1	−2.0	0.02
Depression	4.9	4.6	NS	−2.2	−1.7	NS	−3.0	−1.1	0.002

EQ-5D, 5-dimensional EuroQol; Hb, hemoglobin; RAND-36, RAND 36-item health survey; VAS, visual analogue scale; NS, not significant.
[a]For difference between groups.
[b]For difference in change between groups.

Table 4. Association between baseline menstrual blood loss, hemoglobin and serum ferritin and change in health-related qualilty of life (HRQoL) measurements: a linear regression analysis.

	Menstrual blood loss		Hemoglobin		Serum ferritin	
	β	*p* value	β	*p* value	β	*p* value
From baseline to 6 months						
Rand-36						
General health	−0.07	NS	−0.11	NS	−0.03	NS
Physical functioning	−0.06	NS	−0.28	0.001	0.14	NS
Mental wellbeing	0.07	NS	−0.16	NS	0.06	NS
Social functioning	0.10	NS	−0.13	NS	0.07	NS
Energy	0.08	NS	−0.23	0.005	0.07	NS
Pain	−0.05	NS	−0.04	NS	−0.06	NS
Role functioning physical	0.05	NS	−0.14	NS	0.18	0.02
Role functioning mental	0.08	NS	−0.14	NS	0.07	NS
EQ-5D	0.08	NS	−0.08	NS	0.19	0.01
VAS	−0.02	NS	0.05	NS	−0.05	NS
Anxiety	−0.07	NS	−0.13	NS	0.45	<0.001
Depression	0.04	NS	0.15	NS	0.05	NS
From baseline to 12 months						
Rand-36						
General health	−0.06	NS	−0.06	NS	−0.03	NS
Physical functioning	−0.01	NS	−0.26	0.002	0.10	NS
Mental wellbeing	−0.004	NS	−0.20	0.02	0.03	NS
Social functioning	0.10	NS	−0.18	0.03	0.07	NS
Energy	0.08	NS	−0.31	<0.001	0.04	NS
Pain	0.00	NS	−0.03	NS	0.03	NS
Role functioning physical	0.10	NS	−0.15	NS	0.11	NS
Role functioning mental	0.02	NS	−0.19	0.02	0.06	NS
EQ-5D	−0.01	NS	0.01	NS	0.03	NS
VAS	0.06	NS	−0.06	NS	−0.12	NS
Anxiety	0.05	NS	0.24	0.004	−0.021	NS
Depression	0.09	NS	0.28	0.001	0.01	NS

β, standardized coefficients beta; EQ-5D, 5-dimensional EuroQol; RAND-36, RAND 36-item health survey; VAS, visual analogue scale; NS, not significant.

hemoglobin and score change in anxiety ($p = 0.004$) and depression ($p = 0.001$) was also found, indicating fewer symptoms after treatment with lower baseline hemoglobin. Baseline ferritin showed no correlations 12 months after the treatment.

Discussion

After treatment of HMB, HRQoL increased more in initially anemic than in nonanemic women, indicating that the increase of HRQoL is linked to correction of anemia. However, only 8% of anemic women took iron supplementation at baseline. Correction of anemia and iron deficiency after treatment of HMB took a long time. After 1 year, hemoglobin was still lower among anemic compared to nonanemic women and correction of ferritin took 5 years.

Several previous studies have shown a decreased HRQoL among anemic or iron-deficient women of reproductive age. Ando et al. (12) found decreased vitality and general health scores in 92 anemic premenopausal women compared with national norms. After iron therapy, all domain scores increased. Grondin et al. reported significantly reduced general health scores in 105 severely iron-deficient menstruating students compared with 376 iron-sufficient (ferritin ≥20 μg/L) students, but did not find differences in other SF-36 dimensions (13). De Souza investigated connections between HMB, anemia and HRQoL in 58 women with 6 month's follow up, and found positive correlation between hemoglobin and SF-36 scores before HMB treatment (23).

We did not find differences in HRQoL between anemic and nonanemic women at baseline measured by a variety of HRQoL instruments. However, after treatment, HRQoL increased more among anemic than among nonanemic women. In multivariate analysis, there was a strong correlation between improvement of HRQoL and pretreatment hemoglobin, but not with pretreatment menstrual blood loss. The subjective experience of HMB may outweigh the symptoms of anemia at baseline and explain group similarities, but improvement of HRQoL after treatment seems strongly associated with correction of anemia.

No differences were found in HRQoL between different ferritin groups at baseline or after treatment, but this does not directly mean that iron deficiency had no effect on HRQoL. We compared groups with severely low and higher ferritin. It is now recognized that ferritin <15 μg/L is severe iron deficiency and that some deficiency continues up to 50 μg/L. To detect differences between iron-deficient and truly iron-sufficient groups, women with ferritin <15 μg/L should be compared with women with ferritin ≥50 μg/L. In our study only six women had ferritin ≥50 μg/L, not permitting such comparisons.

Our study showed that although anemia was corrected during the first year after treatment of HMB in most women, it took several years to refill the iron stores with normal dietary iron. A major surprise was that only a small number of anemic women were given iron substitution. A possible explanation for low supplementation is that clinicians focus solely on treatment of HMB itself, and may not pay specific attention to diagnosis and treatment of anemia and iron deficiency. Many doctors anticipate that anemia and iron deficiency will spontaneously correct once HMB is adequately treated. This study indicates that correction may actually take considerable time, so it is recommended to treat all women with anemia or iron deficiency and HMB with an effective and rapidly assimilated modern iron preparation at initiation of HMB therapy.

This study has limitations, as a secondary analysis of the randomized HMB study. Usage of RAND-36 as a measurement of HRQoL may have limitations to detect differences in quality of life in women with HMB, because while still a validated metric, it is not condition-specific. Other reasons than HMB may also have affected hemoglobin or ferritin values. However, we checked women's histories and there were no differences between the groups in terms of other anemia causes. Number of anemic women was limited and the low ferritin group would have been better compared with women with ferritin >50 μg/L. Despite limitations, the major strength of this study was that a variety of available validated instruments were used to measure the HRQoL. Second, the study population reflects treatment of HMB in the whole country and follow-up was long.

Conclusions

Reasons for reduced quality of life among women with HMB are complex, and are not explained by anemia or iron deficiency alone. However, our study showed, that after HMB treatment, HRQoL increased more in anemic than in nonanemic women. Previous studies have shown increase in HRQoL after treatment of anemia and iron deficiency by iron substitution in reproductive age women (12,15). Our study together with these other studies emphasize the importance of treatment of anemia and iron deficiency by early iron substitution as an integral part of treatment of HMB.

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