

Comparative effectiveness and impact on health-related quality of life of hysterectomy vs. levonorgestrel intra-uterine system for abnormal uterine bleeding

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Abstract. – OBJECTIVE: To compare hysterectomy and levonorgestrel intra-uterine system (LNG-IUS) for the treatment of abnormal uterine bleeding (AUB) and iron deficiency anemia.

PATIENTS AND METHODS: Retrospective study evaluating quality of life, sexual function, satisfaction and blood hemoglobin concentration improvement in 60 pre-menopausal women treated with hysterectomy or LNG-IUS. All analysis was performed with statistical software SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS: Despite superior control of bleeding and dysmenorrhea observed after hysterectomy, LNG-IUS showed similar impact on blood hemoglobin levels, quality of life, satisfaction and sexual function resulting more cost-effective.

CONCLUSIONS: In the absence of contraindications, LNG-IUS should always be the first therapeutic choice for chronic AUB. Surgical treatment must be considered as an “extrema ratio”.

Key Words:

Abnormal uterine bleeding (AUB), Iron deficiency anemia, Hysterectomy, Levonorgestrel intra-uterine system (LNG-IUS), Quality of life (QoL), EQ-5D.

plasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified³. AUB has a negative impact on the quality of life and is a common cause of iron deficiency anemia. It represents one of the most frequent gynecological diseases of the reproductive age, counting 70% of visits in premenopausal women^{3,4}. The levonorgestrel-releasing intrauterine system is a device that releases 20 µg/d of levonorgestrel over 5 years and in a recent study shows a reduction of menstrual bleeding in 72.7% and amenorrhea in 13.6% of women at 6 months⁵. Surgical management of abnormal uterine bleeding means still the definitive treatment, but it's not free from surgical risks and important costs. The aim of this study is to compare the efficacy and the cost-effectiveness of hysterectomy and LNG-IUS in managing an abnormal uterine bleeding in premenopausal women with iron deficiency anemia. The patients were evaluated for serum levels of hemoglobin at the time of treatment and at 6 months. Secondary outcomes evaluated sexual health, dysmenorrhea and improvement of the quality of life (QoL) through the European 5-Dimensional Euro Qol questionnaire⁶.

Introduction

Abnormal uterine bleeding (AUB) is defined, according to the International Federation of Gynecology and Obstetrics (FIGO), as any alteration in frequency, duration or volume of menstrual blood flow^{1,2}. Lack of uniformity and confusion, with several terminologies used to define uterine bleeding, has been supplied by the FIGO working group in 2011, with the introduction of the PALM-COEIN classification. This system groups the causes of AUB through an acronym: polyp, adenomyosis, leiomyoma, malignancy and hyper-

Patients and Methods

This retrospective study investigated 60 premenopausal women, whose median age was of 45,2, with abnormal uterine bleeding treated in our hospital from January 2014 to January 2015. The Ethical Committee of the Sapienza University approved this investigation. The study included 2 groups: Group A comprised 30 patients who underwent abdominal hysterectomy (respectively 16

to total hysterectomy and 14 to supracervical hysterectomy). All patients, in which hysterectomy was performed in emergency or association with bilateral oophorectomy, were excluded. Group B included 30 patients treated with LNG-IUS. Exclusion criteria were the assumption of pharmacological treatment for AUB in the previous 3-month and uterine malignancy. All patients with other causes of anemia, adnexal disease, atypical endometrial hyperplasia, endometrial cancer, abnormal cervical Pap smear were previously excluded from the trial. All patients enrolled had iron deficiency anemia (Hb < 12 g/dl). Demographic, anamnestic and objective data were abstracted from medical records; baseline menstrual patterns, hemoglobin values, chronic diseases and drugs associated with AUB were recorded for both groups. Evaluation of menstrual blood loss was assessed semi-quantitatively by Pictorial Blood Loss Assessment Chart (PBAC), as described by Higham et al⁷, and women with heavy menstrual bleeding had a score > 100. To evaluate the quality of life, sexual health and dysmenorrhea before treatment and after 6 months, the participants were called to fill out a questionnaire. Quality of life was assessed by 5-Dimensional Euro Qol (EQ-5D), a standardized questionnaire divided into 2 sections: the first one analyzes 5 statements about self-reported health state, the second one includes a visual-analogue scale (VAS) ranged from 0 (worst imaginable health state) to 100 (best imaginable health state)^{6,8}. In all participants we evaluated sexual health assessing the prevalence of “decrease of libido” and “vaginal dryness” after 6 months. Among women with regular intercourses, we also measured the intensity of dyspareunia by using a 100-mm visual analogue scale (VAS) at the beginning and after 6 months. Dysmenorrhea associated with AUB has been estimated using the same method performed to quantify dyspareunia at baseline and at 6 months from the onset of treatment. Finally, we asked the patients to express their level of satisfaction about treatment through an evaluation scale graduated by 0 (dissatisfaction) to 5 (high satisfaction).

Statistical Analysis

Statistical analyses were performed with SPSS version 21 (SPSS Inc., Chicago, IL, USA). The tests performed were the Pearson χ^2 -test to evaluate the relationship between nominal variables and Student's *t*-test for the analysis of independent and paired samples. A level of $p < 0.05$ was considered to be statistically significant.

Results

Our study was composed of 60 women divided into two groups according to the type of treatment: 30 patients underwent to hysterectomy (group A) and 30-inserted LNG-IUS. The mean age of participants was 45.2 years (SD 4.5); group A median age was significantly higher than group B, respectively 46.7 and 43.8 years. Median value of BMI was 25.0 (SD 4.6). The total number of delivery among the 60 patients was 102 (from 0 to a maximum of 3 deliveries), nevertheless 7 patients had no pregnancy. In brief, 41.2% of deliveries were carried out with caesarean section, while 58.8% occurred spontaneously. It has been investigated the coexistence of chronic pathologies (hypertension, diabetes mellitus, coagulopathy, thyroid dysfunction) that may potentially cause AUB and 28 patients (46.7%) showed this association. No association was proved between the variables presence/absence of pathologies and the type of treatment through the application of the χ^2 -test. Furthermore, we found that 38.3% of patients took drugs quoted in PALM-COEIN system as cause of AUB (sodium levothyroxine, anticoagulant, antiepileptic and tricyclic antidepressant drugs). No statistical difference has been noted between the variable drug assumption (yes/no) and the specific treatment. According to the typology of AUB, 40 women had heavy menstrual bleeding (HMB), 9 an inter menstrual bleeding (IMB) and 11 a prolonged menstrual bleeding (PMB). By analyzing etiological diagnosis of abnormal uterine bleeding, the patients have been divided into three groups: I, leiomyomas; II, leiomyomas and adenomyosis; III, various causes of AUB, such as ovulatory dysfunction, endometrial dysfunction and endometrial hyperplasia. At the basal evaluation, dysmenorrhea was reported by the 66.7% of total sample (40 patients). Particularly, the symptom was present in the 60% of the patients belonging to the group A and in the 73.3% of the patients assigned to the group B, although no significant association was found when the groups are compared ($p > 0.05$). Before treatment, all participants were asked to rate dysmenorrheal severity by using a visual analogue scale (VAS) from 0 (no pain) to 10 (most intense pain). In brief, in the group A, the mean score was 5.00, while in the group B was 5.67. Pain was reevaluated at 6 months only in LNG-IUS users and it decreased of 75,3% (VAS 1,40; $p < 0.001$). 81.7% of patients (49) declared to have regular sexual activity: among these women, 32% in-group A

and 37.5% in-group B declared to suffer from dyspareunia. The difference in dyspareunia VAS score variation between 0 and 6 months post-treatment showed a decrease of 71% in both two-study groups ($p<0.01$). Sexual health was also investigated evaluating at 6 months the prevalence of sexual desire disorders and vaginal dryness in all patients. Hypoactive sexual desire was detected in 30% of group A and 20% of group B, while 14 women experienced vaginal dryness (respectively 8 and 6 in the two groups). Therefore, we analyzed the recurrence of “vaginal dryness” in subjects undergone to total vs. supracervical hysterectomy, showing an almost significant association ($p=0.051$). It has been observed that total hysterectomy was more frequently associated with this symptom. Before treatment, the characteristics of the menstrual cycle, in terms of duration and quantity of flow, were assessed in the two groups. The findings indicated that menstrual flow was 8.3 and 7.5 days in-group A and B with no significant differences. The entity of the menstrual loss in the group B measured with PBAC was reduced from a mean score of 206.10 to 42.67 at subsequent time point ($p<0.001$). In LNG-IUS users, both quantity and duration of menstrual cycle were reduced after 6 months (respectively -79% and -68%). On admission to the study, all women included had low blood hemoglobin count, due to excessive menstrual blood loss, the major factor influencing the iron balance in women. Mean baseline hemoglobin was < 12 g/dl in both groups. Serum hemoglobin increased during the 6 months

after treatment of AUB from 9.56 g/dl to 12.58 g/dl in-group A and from 10.16 g/dl to 12.69 g/dl in-group B. When comparing treatment options (LNG-IUS and hysterectomy) no remarkable differences in hemoglobin concentrations were identified after 6 months ($p>0.05$). At 6 months a greater proportion of patients achieved the primary endpoint with a resolution of the anemic state (respectively 86.66% in group A and 90% in group B). Participants were asked to record through a multiple-choice question whether they considered that an adverse reaction had occurred and the results are shown in Table I. In the whole study population and in-group A the most frequent side effects were decreased libido and vaginal dryness. Spotting was described as the most common adverse reaction in LNG-IUS users. To describe findings of the effects of the two treatments on quality of life, a validated questionnaire (EQ-5D) was used^{6,8}. According to current indications, a synthetic score has been calculated for representing perceived health state among interviewed patients. There were no differences in the baseline EQ-5D scores between group A and B: the middle values of the EQ-5D synthetic score obtained from the two groups of patients were 0.418 in the group A and 0.509 in the group B. After 6 months, patients in both treatment groups showed broad improvement in health-related quality-of-life scores, resulting 0.867 and 0.891, respectively. Data from EQ5D demonstrated that the higher was the middle value, the better was health state. We calculated the percentage frequencies at baseline

Table I. Side effects referred after hysterectomy and LNG-IUS.

Side effects	Hysterectomy (% answers) (% cases)	LNG-IUS (Mirena) (% answers) (% cases)	Total amount (% answers) (% cases)
Decreased libido	9 (24.3%) (47.4%)	5 (11.6%) (20.8%)	14 (17.5%) (32.6%)
Vaginal dryness	8 (21.6%) (42.1%)	6 (14.0%) (25.0%)	14 (17.5%) (32.6%)
Spotting	--	12 (27.9%) (50.0%)	12 (15.0%) (27.9%)
Dyspareunia	4 (10.8%) (21.1%)	3 (7.0%) (12.5%)	7 (8.8%) (16.3%)
Cyclical pelvic pain	6 (16.2%) (31.6%)	--	6 (7.5%) (14.0%)
Depression	4 (10.8%) (21.1%)	1 (2.3%) (4.2%)	5 (6.3%) (11.6%)
Amenorrhea	--	3 (7.0%) (12.5%)	3 (3.8%) (7.0%)
Headache	--	3 (7.0%) (12.5%)	3 (3.8%) (7.0%)
Abdominal bloating	1 (2.7%) (5.3%)	2 (4.7%) (8.3%)	3 (3.8%) (7.0%)
Breast tenderness	--	3 (7.0%) (12.5%)	3 (3.8%) (7.0%)
Others	5 (13.5%) (26.3%)*	5 (11.6%) (20.8%)**	10 (12.5%) (23.3%)
Total	37 (100.0%) (194.7%)	43 (100.0%) (179.2%)	80 (100.0%) (186.0%)

*5 patients undergone to hysterectomy referred: anxiety (1), lower urinary tract dysfunctions (2), intestinal dysfunctions (1), sciatalgia (1).

**5 patients submitted to LNG-IUS insertion referred: anxiety (1), dysmenorrhea (2), IUS expulsion (1), IUS removal due to spotting.

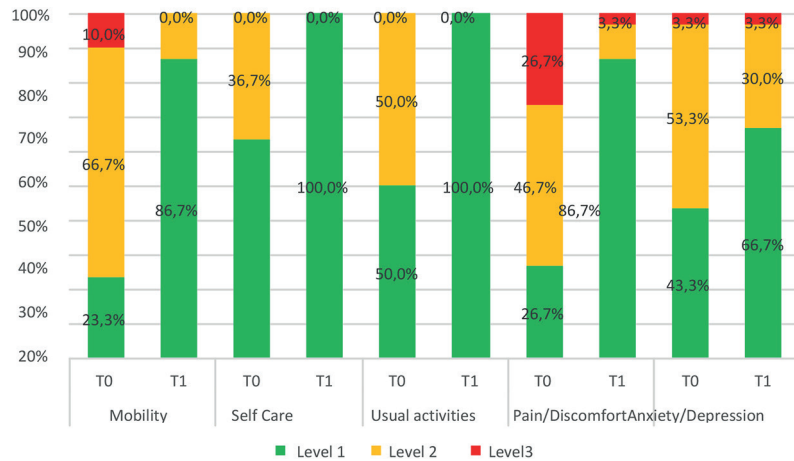


Figure 1. Percentage frequencies of gravity levels in 5 dimensions of EQ-5D at time T0 (baseline) and T1 (after 6 months). Group A, patients undergone to hysterectomy.

and T1 for all levels of each dimension of EQ-5D in the two subgroups of patients (Figure 1-2). For instance, the percentage frequencies of level 1 (any problem) sensitively increased in-group A and B between the two times of observation (mobility rate from 23.3% to 86.7% in-group A, from 23.3% to 93.3% in-group B). Besides, perceived health state was measured with a VAS score ranged from 0 to 100. At baseline the middle values noticed in the two groups were 45.47 (group A) and 50.67 (group B). At 6 months they increased to 84.83 and 84.00, respectively. From statistical analysis the middle values among baseline

and after treatment were meaningfully different ($p < 0.001$). The satisfaction rate, examined after 6 months, had a mean score of 4,17 in-group A and 4,50 in-group B.

Discussion

AUB affects up to 30% of women during their reproductive years and has an important impact on physical, psychological and emotional status⁹⁻¹¹. For many decades hysterectomy has been considered the standard treatment of AUB. Al-

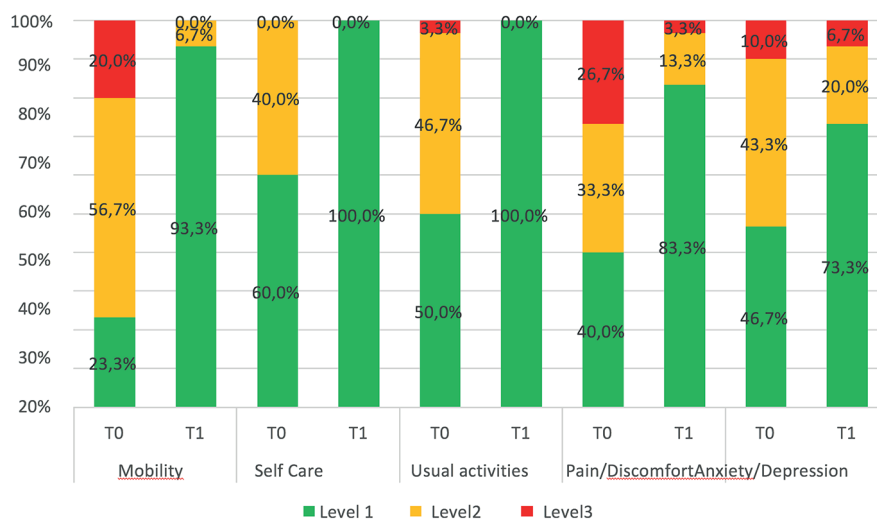


Figure 2. Percentage frequencies of gravity levels in 5 dimensions of EQ-5D at time T0 (baseline) and T1 (after 6 months). Group B, patients that inserted levonorgestrel-IUS (Mirena®).

though it induces a high rate of satisfaction, it's burdened with potential risks such as irreversible loss of fertility, negative psychological impact, post-surgical morbidity, mortality and urinary incontinence. Evidence suggests that hysterectomy could induce long-term effects on ovarian function due to intra-ovarian artery blood flow reduction¹². Otherwise, LNG-IUS has a lower impact on ovarian function, representing the most appropriate choice among patients asking for a contraceptive and fertility-sparing therapy¹³. The guidelines of National Institute for Health and Clinical Excellence (NICE) declare that, in absence of contraindications, the insertion of LNG-IUS represents the first-choice therapy in management of AUB. Therefore, hysterectomy should be suggested in those patients in whom conservative therapies have been refused, are contraindicated or ineffective^{14,15}. Data evidence that no significant differences and statistical associations exist between the two treatments, while the comparison between basal and post-treatment evaluation is significant. Although LNG-IUS is not equivalent to hysterectomy in treating dysmenorrhea, our study has shown that 2/3 of patients referred resolution or reduction of their symptom, while only 6.66% of patients reported a worsening of menstrual pain. Despite the positive outcomes on dyspareunia, results from our analysis of sexual items proved the onset of vaginal dryness and reduced sexual desire both after surgery and medical therapy. Patients treated with LNG-IUS experienced a significant change in menstrual pattern: duration of menstrual cycle decreased from a mean of 7.5 to 2.5 days. One patient of group B with recurrent spotting, the most frequent reason associated with early interruption of treatment, removed IUS after 5 months. Amenorrhea occurred only among 10% of LNG IUS-users: nevertheless, the interruption of menstrual flow, sometimes producing discomfort on women, improves the condition of anemia. It has been observed that 7 women didn't resolve their anemic state: between them, 3 had been submitted to hysterectomy and 3 had been treated by LNG-IUS (1 woman removed the intrauterine system due to spotting and another woman had spontaneous expulsion). The persistence of anemia in the remaining 5 patients may suggest not diagnosed causes such as gastritis, celiac disease and peptic ulcer disease¹⁶. In a single patient belonging to the Group B, after a spontaneous expulsion of the device, it has been necessary the surgery to resolve the anemic condition. Among the group A the incidence of adverse effects was

63.3%, while in the group B was 80%. Nevertheless the mean level of satisfaction after 6 months of therapy was high for both the groups, since the 81.6% of patients referred a score of 4 or 5. These data showed that adverse effects associated with the treatment, although very frequent, were well tolerated in patients. Given the above, it may be concluded that intrauterine system is as effective as hysterectomy in treating patients with iron-deficiency anemia due to AUB. In brief, even though surgery was identified as the most effective choice in reducing dysmenorrhea and menstrual blood loss, both QoL and hemoglobin concentrations were likewise increased in the two groups.

Conclusions

Data suggest as medical therapy positively acts on women's health. Further advantages of hormonal system are the fertility-sparing use, high contraceptive effectiveness, minimum interference on hormone balance, long duration of action, ease of use and few side effects. An additional factor sustaining the use of LNG-IUS is represented by the cost-effectiveness: a randomized trial 5 year follow up by Hurskainen et al⁹ analyzed the costs of medical and surgical therapy for management of AUB. After one year, the results suggested an economic burden for hysterectomy 3 times more expensive than LNG-IUS. After 5 years, treatment with the LNG-IUS was still 40% less expensive than hysterectomy. The discounted direct and indirect costs in the LNG-IUS group remained substantially lower than in the hysterectomy group. This study shows that both LNG-IUS and hysterectomy improve EQ-5D. However, LNG-IUS compared with a hysterectomy has similar effects with lower costs and complications rate. In conclusion, the clinical approach to AUB should begin from a detailed evaluation of subjective symptoms due to iron deficiency, such as asthenia, impaired concentration, personal and socio-occupational consequences. Moreover, the therapy of chronic AUB should be personalized according to clinical presentation and patients' expectations. Hysterectomy should always be considered as an "extrema ratio", since uterine preservation is advisable at any age for prevention of pelvic floor dysfunctions, psychological and sexual disorders, as well as to ensure intra-ovarian blood flow.

Conflict of interest

The authors declare no conflicts of interest.

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