

## Original study/Estudo original

# Levonorgestrel intrauterine device effectiveness in heavy menstrual bleeding treatment in obese women

## Efetividade do dispositivo intra-uterino de levonorgestrel no tratamento de hemorragia uterina anómala em mulheres obesas

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### Abstract

**Objective:** We aimed to identify if there was any difference in Levonorgestrel-releasing intrauterine system (LNG-IUS) efficacy or weight gain when used in heavy menstrual bleeding (HMB) treatment, between obese and non-obese women.

**Population and methods:** This was a case-controlled retrospective study undertaken between 2002-2007. 194 women with HMB were treated with LNG-IUS and stratified into two groups accordingly with body mass index (BMI): Obese Group – BMI  $\geq 30$  (n=53) and Non-obese Group – BMI  $< 30$  (n=141). Age, weight, days of spotting and days of menses were analyzed at 1, 3 and 6 months after insertion and then annually until 2 years. Analytic parameters of anemia (hemoglobin, serum ferritin, mean corpuscular volume) were reviewed at pre-insertion, at 6 months and then annually until 2 years.

**Results:** During the 2-year follow-up there was a similar improvement in two groups regarding duration of menses, *spotting* and in analytic parameters of anemia. A statistically significant improvement was observed in obese group after 2 years of treatment regarding analytic parameters of anemia and menstrual characteristics, without weight gain.

**Conclusion:** In obese women, the LNG-IUS is an effective treatment for heavy menstrual bleeding, without being associated to weight gain.

**Keywords:** Levonorgestrel-releasing intrauterine system; Obesity; Body mass index; Heavy menstrual bleeding; Anemia.

### OVERVIEW AND AIMS

Obesity is one of the biggest public health problems of the 21st century<sup>1</sup>. The World Health Organization (WHO) defines obesity when body mass index (BMI) is greater than or equal to 30 Kg/m<sup>2</sup><sup>1,2</sup>. The last estimates affirm that obesity has more than doubled since 1980, with nearly 30-70% of European adults being overweight and 10-30% being obese<sup>1</sup>. Weight excess confers a higher risk of diabetes, cardiovascular disease and cancer (including endometrial cancer) and besides being a public health problem, contributing to elevated costs in health, it imposes new challenges in the treatment of many diseases<sup>2</sup>. Metabolic changes in obesity and a higher body mass index may lead to reduced effectiveness of many drugs in which hormonal

contraceptives are an example, but nevertheless is still controversial<sup>3,4</sup>.

Heavy menstrual bleeding (HMB), also named menorrhagia, is defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life<sup>5,6</sup>. It affects 4-51.6% of women. However, the real prevalence is unknown, because the studies available are very heterogeneous in what concerns the population and the criteria (personal perception of excessive menstrual blood loss (MBL) or objective as MBL  $> 80$ mL) that were used<sup>5</sup>. HMB increases with age, being more frequent in the perimenopausal period<sup>5,6</sup>. Other risk factors for HMB are the presence of uterine fibroids, blood disorders, endometriosis, adenomyosis, smoking and high alcohol consumption<sup>5</sup>. Obesity has been associated with dysfunctional uterine bleeding, secondary amenorrhea and polycystic ovary syndrome<sup>2,7,8</sup>.

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Medical treatment of HMB includes the levonorgestrel-releasing intrauterine system (LNG-IUS), oral and injectable progestins, danazol, non-steroidal anti-inflammatories and tranexamic acid<sup>2,5-9</sup>. Surgical alternatives are available when medical treatment has failed<sup>3</sup>. Hysterectomy and endometrial ablation are the surgical solutions available, however they are associated with peri-operative and long-term surgical risks<sup>3-9</sup>.

The LNG-IUS is a T-shaped contraceptive device with a reservoir containing 52 mg of levonorgestrel. It delivers 20 mcg a day and maintains its efficacy for at least 5 years<sup>9,10</sup>. One of its effects is endometrial suppression, without ovulation inhibition<sup>5-10</sup>. The LNG-IUS has proved to be one of the most effective medical treatments for HMB, by reducing the MBL in 79-87%<sup>5,6,9,10</sup>. Apart from reducing the MBL it has shown to improve anemia analytic parameters that result from HMB<sup>5,6,9,10</sup>. Some previous studies related to the contraceptive effect of LNG-IUS support its use in obese women, however it is associated with a slight increase in weight<sup>3</sup>.

The aim of our study was to compare the use of LNG-IUS in the treatment of HMB between obese and non-obese women. We wished to ascertain if there were any differences in menstrual characteristics, anemia analytic parameters and weight between the two groups of women.

## STUDY DESIGN, POPULATION AND METHODS

This was a retrospective, case-control study, performed between 2002 and 2007.

Using a clinical database, we identified all women in reproductive age, aged  $\geq 18$  years, with HMB who underwent LNG-IUS insertion, between 1<sup>st</sup> January 2002 and 31 December 2007. We chose this time frame because during this period, at our institution, there was a specific medical appointment destined to follow-up women with HMB who were treated with LNG-IUS. HMB was defined as excessive menstrual blood loss that interfered with women's quality of life. The etiology of HMB was classified according to PALM-COEIN classification (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified)<sup>11</sup>. Women who chose LNG-IUS as a way of treatment for their HMB were scheduled for that medical appointment, where the insertion and a protocol of follow-up were performed. The LNG-

-IUS was inserted within 7 days of the onset of menstruation. The follow-up protocol approved at our institution included an appointment at the LNG-IUS insertion clinic, at 1, 3 and 6 months and then annually until discharge from the hospital or LNG-IUS removal.

The WHO's criterion for anemia in non-pregnant adult women is an hemoglobin value of less than 12.0 g/dL, and was the value admitted for diagnosis of anemia.<sup>12</sup> The anemia parameters, such as hemoglobin, ferritin and mean globular values, were recorded in all patients and not only in patients with anemia diagnosis.

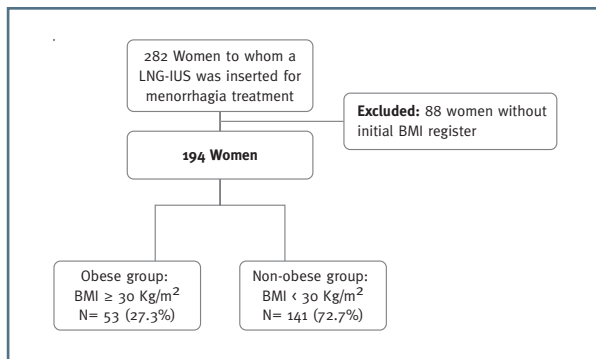
We considered two groups: in obese group were included women who had a first appointment mean body index (BMI)  $\geq 30$  Kg/m<sup>2</sup> and in non-obese group women who had BMI  $< 30$  Kg/m<sup>2</sup>. The parameters analyzed were: age, number of days of spotting, number of days of menses and weight at month 1, 3 and 6 and then annually until the second year. The anemia parameters (hemoglobin, ferritin and mean globular volume) were analyzed at insertion, at month 6 and then annually for 2 years. We also analyzed the rate of expulsion, reasons for removal and the number of hysterectomies performed. Women who didn't have the register of BMI were excluded from analysis. We considered a 2-year interval for analysis because there was very little data available after year 2. Besides comparing the different parameters between the two groups, we compared in the obese group the different parameters at year 2 with pre-insertion values, in order to verify if LNG-IUS is effective in the treatment of HMB in this group. We did not compare the same values in the non-obese group because LNG-IUS efficacy is already well established<sup>13</sup>. The data were collected by consulting clinical files.

The statistical analyses were performed with SPSS statistical software (version 14.0; SPSS Inc, Chicago, IL). The Wilcoxon test was applied to dependent variables, the Mann-Whitney test was applied to independent samples and the Chi-square test was applied to categorical variables. Probability values of  $< 0.05$  were considered statistically significant.

## RESULTS

### Subject disposition and demographic characteristics

Out of the 282 LNG-IUS inserted for HMB treatment, 194 women met the inclusion criteria and were



**FIGURE 1.** Population of the study

divided in two groups according to their initial BMI, Figure 1.

The mean age of participants was similar in both groups (obese group: 44.17±5.4, non-obese group: 43.52±5.0, p=0.434).

The etiology of HMB was similar in both groups, being adenomyosis the most frequent diagnosis, 52.8% and 47.5% in obese and non-obese groups respectively, followed by leiomyomas, 26.4% and 33.3% in obese and non-obese groups respectively. Unexpectedly, polyps were only present in non obese women, however, 70% of these were present in women with BMI in the overweight range (25-30 Kg/m<sup>2</sup>). Others diagnosis included in the PALM-COEIN classification had no expression in this series and were excluded from analysis. The frequencies of HMB etiology is presented in Table I.

**Menstrual characteristics**

Analyzing the medical profiles, we could not obtain the baseline days of menses and days of spotting. How-

ever, when we analyzed the days of menses during the 2 years after insertion we observed that the days of menses and days of spotting progressively decreased in both groups, in a similar way (Table II). When we compared the mean days of menses and spotting at month 1 with year 2 only in the obese group, we observed a significant decline (Table V).

**Anemia analytic parameters**

At the baseline, the mean hemoglobin levels were similar in both groups, 12.36 g/dL and 12.44g/dL, in obese and non-obese women respectively (Table III); 36.7% had anemia in obese group compared to 33.8% in non-obese group, p=0.729. During the two years of follow-up, the mean values of hemoglobin registered a progressive rise in both groups (Table III). When we analyzed the difference between the values of hemoglobin at year 2 with pre-insertion values, the main gain of hemoglobin was 1.02 and 3.55, in obese and non obese group respectively, being the difference between the two groups not statistically significant, p=0.128 (Table III). After 2 years there were no values of Hb below 12g/dL in both groups. In the obese group there was a significant gain in hemoglobin after two years, rising from 12.36g/dL to 13.66g/dL, p=0.004 (Table V).

With respect to ferritin, we observed a similar progressive rise in ferritin mean values in both groups, rising from 29.01 and 23.30 at baseline to 71.87 and 55.74 after 2 years in obese and non-obese group respectively (Table III). The mean gain in ferritin in obese group after 2 years was 45.21, p=0.001 (Table V).

The mean corpuscular volume (MCV) values at the baseline were similar in both groups, 83.04 fL and 84.79 fL, in the obese and non-obese women respecti-

**TABLE I. ETIOLOGY OF HBM ACCORDING TO PALM-COEIN CLASSIFICATION**

	Obese	Non obese	P- value
Adenomyosis	28 / 52.8%	67 / 47.5%	0.438
Leiomyomas	14 / 26.4%	47/ 33.4%	0.388
Ovulatory Dysfunction	9 / 17%	13 /9.2%	0.117
Polyps	0 / 0%	10 / 7.1%	0.048
Not classified	2/ 3.8%	4 / 2.8%	0.720
Total	53 / 100%	141 / 100%	

Legend: HMB, heavy menstrual bleeding; PALM-COEIN classification: polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified. Malignancy and hyperplasia, coagulopathy and iatrogenic categories were excluded from analysis

**TABLE II. MEAN CHANGE IN DAYS OF MENSES AND DAYS OF SPOTTING DURING THE TWO YEARS AFTER LNG-IUS INSERTION**

		Obese		Non-obese		p value
		n	Mean±SD	n	Mean±SD	
Days of menses	Month 1	41	4.17±4.83	105	4.23±4.64	.740
	Month 3	37	3.46±3.73	85	3.58±4.14	1
	Month 6	39	3.44±4.94	93	2.65±2.98	.933
	Year 1	30	2.10±2.67	83	2.02±2.80	.778
	Year 2	19	2.26±3.25	50	2.26±5.25	.423
	Year 2 – Month 1	21	-0.67±4.45	50	-1.60±6.31	.239
Days of spotting	Month1	41	9.24±9.68	105	10.58±9.65	.390
	Month 3	36	3.33±5.138	86	6.06±8.20	.100
	Month 6	39	3.49±7.56	91	2.98±4.45	.124
	Year 1	30	1.50±5.42	83	1.33±3.03	.366
	Year 2	22	0.32±0.95	58	1.21±3.59	.335
	Year 2 – Month 1	21	-10.5±9.65	51	-10.0±1.20	.985

SD: standard deviation.

**TABLE III. MEAN CHANGE IN ANALYTIC PARAMETERS OF ANEMIA**

		Obese		Non-obese		p value
		n	Mean±SD	n	Mean±SD	
Hemoglobin	Pre-insertion	49	12.36±1.69	139	12.44±1.48	.963
	Month6	36	13.04±1.32	77	13.20±1.27	.344
	Year 1	31	13.61±1.02	84	13.50±1.24	.845
	Year 2	19	13.66±0.92	49	15.94±14.34	.301
	Year 2 – Pre-insertion	18	1.02±1.37	49	3.55±14.36	.128
Ferritin	Pre-insertion	46	29.01±38.39	126	23.30±24.07	.460
	Month 6	33	32.71±31.91	69	31.87±40.35	.723
	Year1	29	44.35±34.14	80	34.22±31.68	.133
	Year2	18	71.87±72.70	41	55.74±40.32	.397
	Year 2 – Pre-insertion	18	45.21±56.06	41	34.75±33.62	.850
MCV	Pre-insertion	50	83.04±8.17	136	84.79±9.76	.065
	Month 6	35	82.72±13.16	75	85.42±9.66	.252
	Year 1	31	83.86±12.80	81	87.25±10.28	.013*
	Year 2	19	85.55±10.25	48	89.85±3.72	.023*
	Year 2 – Pre-insertion	19	3.04±14.26	47	4.95±6.44	.848

MCV: Mean corpuscular volume; SD: standard deviation, \* = p&lt;0.05, statistically significant

vely. During the two years, a rise in MCV values in both groups was observed, with a mean gain of 3.04 fL and 4.95 fL in obese and non-obese group respectively (Table III). When we compared the mean value of MCV at year 2 with the pre-insertion mean value in the obese group, we observed a significant rise, being 83.04fL at pre-insertion and 85.55fL after 2 years,

p=0.006 (Table V).

### Weight gain

At the LNG-IUS insertion, the mean weight in the obese group was 87.16 Kg as opposed to the non-obese group where the mean weight was 64.62Kg, p<0.001. When we analyzed the weight gain during the 2 years

**TABLE VI. AVERAGE WEIGHT GAIN DURING THE 2 YEARS AFTER LNG-IUS INSERTION**

		Obese		Non-obese		p value
		n	Mean±SD	n	Mean±SD	
Weight Gain	Month 1	41	0.37±1.18	96	0.15±4.93	.939
	Month 3	36	-0.35±3.05	82	1.08±3.50	.070
	Month 6	34	0.15±2.95	75	0.65±2.92	.839
	Year 1	29	-0.60±6.16	70	0.39±3.39	.865
	Year 2	14	1.14±3.15	33	-0.21±2.95	.216

: Standard deviation. \*= p<0.05, statistically significant

**TABLE V. AVERAGE CHANGE IN DIFFERENT PARAMETERS BEFORE OR DURING THE FIRST MONTH AFTER LNG-IUS INSERTION IN OBESE WOMEN WITH MENORRHAGIA**

Parameters		Obese women		P value
		n	Mean±SD	
Days of menses	Month 1	41	4.17±4.83	.043*
	Year 2	22	2.26±3.25	
Days of spotting	Month 1	42	9.24±9.68	<0.001*
	Year 2	22	0.32±0.95	
Hemoglobin	Pre-insertion	49	12.36±1.69	.004*
	Year 2	19	13.66±0.92	
Ferritin	Pre-insertion	41	29.01±38.39	.001*
	Year 2	9	71.87±72.70	
MCV	Pre-insertion	45	83.04±8.17	.006*
	Year 2	11	85.55±10.25	
Weight	Pre-insertion	53	87.16±12.02	.146
	Year 2	14	86.03±11.54	

MCV: mean corpuscular volume, SD: Standard deviation, \*= p<0.05, statistically significant

after LNG-IUS insertion, we observed that there was almost no increase in weight in either group, registering even a slight decrease (Table IV). When we analyzed the obese group only, the mean weight at pre-insertion was 87.16Kg vs 86.03Kg 2 years after LNG-IUS insertion, p=0.146 (Table V).

### Follow-up

During the two years considered in the study there was a substantial decrease in the number of women in each group. At year 2 there were only 41.5% women in the obese group and 41.1% in the non-obese group when compared to baseline. During the two years there were

10 LNG-IUS expulsions in obese group (18.9%) and 11 in non-obese group (7.8%), p=0.037. Obesity was associated with a 2.75 higher risk of LNG-IUS expulsion when compared to non obese women, (IC 95% 1.09-6.92). In the obese group 13 (18.8%) women were submitted to hysterectomy, compared to 16 (11.4%) women in the non-obese group, all as a consequence of HMB persistence, p=0.014. The relative risk of hysterectomy in the obese group was 2.80, (IC 95%, 1.26-6.26). Eight (15.1%) women were discharge before the 2 years follow-up, all being asymptomatic as well as 39 (27.7%) in non-obese group, all being referred to their family doctor. Seventeen women (12.1%) were lost to follow-up in non-obese group. One woman (1.9%) in the obese group requested LNG-IUS removal, compared to 5 women (3.6%) in non-obese group, p=0.564.

### DISCUSSION

Many papers concerning contraception mention that LNG-IUS can be effective in obese women. However, few studies were performed in order to evaluate if LNG-IUS is effective in HMB treatment in selected obese women<sup>3,5,6</sup>. Our study wishes to evaluate if there are any differences between obese and non-obese women when using LNG-IUS as a treatment option for HMB.

During the two years of follow-up there were no differences between either group concerning the days of menses and the days of spotting. In both groups there was a progressive decrease in the days of menses, which didn't achieve a statistical difference between groups, p=0.239. Nevertheless, the decrease in days of menses and spotting in the obese group after two years of treatment was statistically significant (p=0.043 and



$p < 0.001$ , respectively) which supports LNG-IUS efficacy in HMB treatment in the obese group concerning menstrual characteristics.

Anemia parameters, such as hemoglobin, mean globular volume and ferritin levels improved similarly in both groups during the two years (Table III). Such finding is consistent with the literature, where LNG-IUS has demonstrated to raise hemoglobin, mean globular volume and ferritin levels in women with HMB<sup>5,6,10,14-17</sup>. When we compared the anemia parameters in the obese group, between the baseline and year 2 we found a statistically significant improvement in all parameters (Table V). Once again LNG-IUS seems to be effective in improving anemia parameters in obese women treated for HMB.

Weight gain is sometimes a concern when a contraceptive is initiated and in some cases a reason for early discontinuation. However, in 2011 Lopez et al in a Cochrane review could find only a little evidence in weight gain when progestin-only contraceptives were used, where weight gain was less than 2 Kgs and up to 12 months<sup>19</sup>. Other studies demonstrated that there was no significant weight gain associated with LNG-IUS and one study revealed that LNG-IUS in long term users has been associated with a small increase in weight that was equivalent to the weight gain associated with increasing age<sup>4,18,20</sup>. In our study, the weight gain in both groups didn't reach a statistical difference during the 2 years (weight gain in obese group after 2 years: 1.14, vs -0.21 in non obese group,  $p = 0.216$ ). When we compared the initial and final weight in the obese group we concluded that there wasn't a significant change (initial weight 87.16 vs 86.03 after 2 years,  $p = 0.146$ ). Besides small data, it suggests that LNG-IUS does not provoke weight gain, even in obese women.

LNG-IUS expulsion is the most common cause for failure and occurs in about 5% of users when randomized controlled trials are considered and in about 9.9% when observational studies are taken into account<sup>10,15</sup>. LNG-IUS expulsion occurs mainly in the first year after insertion and is more frequent in nulliparous women, women with severe dysmenorrhea and when inserted immediately after postpartum or post-abortion<sup>10</sup>. In our study, the expulsion rate was 18.9% in the obese group and 7.8% in the non-obese group. The rate of expulsion in the non-obese group is in accordance with the expulsion rate when observational studies are considered. However, the expulsion rate in obese women greatly exceeds the expulsion rate in the

literature. In our study, obesity was associated to a relative risk of 2.75 of LNG-IUS expulsion. A possible explanation for this finding can be a more difficult LNG-IUS insertion in obese women that leads to an incorrect insertion and higher rate of expulsion. However, new prospective larger studies should be conducted to verify if LNG-IUS expulsion rate in obese women is superior when compared with non-obese women.

One limitation of our study is the small data and large number of women who were lost to follow-up. Many of these women abandoned the hospital appointment after being discharged to their family physician, all being asymptomatic (15.1% in obese group and 27.7% in non-obese group). However, LNG-IUS wasn't successful enough to avoid hysterectomy in some women, which accounted 18.8% in obese group and 11.4% in non-obese,  $p = 0.014$ , all because of HMB maintenance. More studies are needed, preferably prospective, including more obese women and stratifying effectiveness with the grade of obesity.

To summarize, the LNG-IUS seems to be an effective option in HMB treatment in obese women, reducing the number of days of menses and spotting and improving anemia analytic parameters, such as hemoglobin, ferritin and mean globular volume. Besides its beneficial effects in HMB treatment, it is also important that LNG-IUS insertion in obese women doesn't seem to be associated with weight gain. However, new prospective, larger studies are needed to prove these findings.

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