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The treatment with Levonorgestrel Releasing Intrauterine System (LNG-IUS) in patients affected by menometrorrhagia, dysmenorrhea and adenomimyois: clinical and ultrasonographic reports

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Abstract. – OBJECTIVE: Adenomyosis is the consequence of the myometrial invasion by endometrial glands and stroma. Transvaginal ultrasonography plays a decisive role in the diagnosis and monitoring of this pathology. Our study aims to evaluate the efficacy of LNG-IUS (Levonorgestrel Releasing Intrauterine System) as medical therapy. We analyzed both clinical symptoms and ultrasonographic aspects of menometrorrhagia and dysmenorrhea in patients with adenomyosis and the control group.

PATIENTS AND METHODS: A prospective cohort study was carried out on 28 patients suffering from symptomatic adenomyosis treated with LNG-IUS. Adenomyosis was diagnosed through transvaginal ultrasonography by an expert sonographer. A control group of 27 symptomatic patients (menorrhagia and dysmenorrhea) without a transvaginal ultrasonographic diagnosis of adenomyosis was treated in the same way. The two cohorts were compared to the efficacy of LNG-IUS on menorrhagia and dysmenorrhea. Patients are evaluated at the time of LNG-IUS insertion and six months after for: increased uterine volume, globulous uterine morphology, uterine symmetry, alterations in the junctional zone, heterogeneous myometrial texture, presence of myometrial cysts, hyperechogenic lines crossing the myometrium, adenomyomas, menstrual blood loss and dysmenorrhea.

RESULTS: After six months, the uterine volume decreased significantly in both cohorts (p=0.005; p=0.005). Furthermore, uterine symmetry, visibility of the junctional zone, heterogeneity of myometrial texture, presence of myometrial cysts, hyperechogenic lines and adenomyomas improved in patients affected by adenomyosis (p>0.001; p>0.001; p>0.001; p=0.014; p=0.025; p=0.014). The blood loss decreased significantly in both the cohorts (p<0.001) and particularly in adenomyotic patients. Pain relief was observed in all the patients (p<0.001).

CONCLUSIONS: LNG-IUS can be considered an effective treatment for managing symptoms and improving uterine morphology.

Key Words:

Benign disease of uterus, Dysmenorrhea, Gynecologic imaging, Leiomyomas of the uterus/adenomyosis.

Introduction

Adenomyosis is a benign gynecological disease with a large variety of clinical manifestation; the most frequent include menorrhagia, metrorrhagia, dysmenorrhea and chronic pelvic pain[1]. Patients can also experience dyspareunia and infertility[2,3]. Its pathogenesis is still unknown, although many theories have been considered over the years[2]. Adenomyosis is histologically defined as the ectopic presence of endometrial glands and stroma in the myometrium, with consequent hyperplasia and hypertrophy of the smooth muscle[4]. Nowadays, a definite diagnosis is still made on a pathological analysis performed on uterine specimens.

Nevertheless, non-invasive image techniques, such as transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI), have proven helpful in the preoperative diagnosis of adenomyosis disease[5-7]. Authors[8,9] who compared the results obtained from TVS and MRI with those

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obtained from histopathology have noticed that MRI and TVS's diagnostic efficiency was almost in line. TVS is considered the first choice of image modality when investigating adenomyosis; however, MRI may be helpful in increasing the diagnostic performance when TVS provides indefinite findings or when dealing with complex cases with the coexistence of other abnormalities (e.g., myomas and severe endometriosis)[10] sonographic diagnosis of adenomyosis is made when at least three of the following signs are found: increased uterine volume, globulous uterine morphology, uterine asymmetry, alterations in the junctional zone, heterogeneous myometrial texture, myometrial cysts and hyperechogenic lines crossing the myometrium. To date, there are not international guidelines for the clinical and surgical management of the pathology. Hysterectomy is a definite treatment of symptomatic patients, but plenty of conservative medical and surgical options can be considered to treat adenomyosis. Adenomyosis, in childbearing age, could be managed with a less invasive approach like medical therapy or conservative surgery. The results obtained from conventional surgery are effective for symptom control. Improve abdominal pain, abnormal uterine bleeding and improve fertility are the main results of this type of surgery[11]. Levonorgestrel Releasing Intrauterine System (LNG-IUS) represents one of the medical alternatives in the treatment of adenomyosis. This device has been approved in Europe as a contraceptive method in 1990; more recently, it has been used to manage menorrhagia and dysmenorrhea[12], abnormal uterine bleeding (AUB), endometrial hyperplasia, adenomyosis[13] uterine fibroids and as a progestin component in postmenopausal hormone therapy[14]. The use of LNG-IUS for five years duration is motivated by the inhibition of the endometrial proliferation induced by the drug, which leads to a positive impact on dysmenorrhea and heavy menstrual bleeding.

Moreover, because of the local administration of the drug (1000 ng/mL intrauterine *vs.* <0.2 ng/mL plasmatic), the device is characterized by low metabolic side effects[15]. Indeed, patients show excellent tolerance and good compliance in the majority of cases[16,17]. With these premises, the objective of this pilot study is to evaluate the efficacy of LNG-IUS as medical therapy to treat both clinical symptoms (dysmenorrhea and heavy menstrual bleeding in particular) and ultrasonographic aspects of adenomyosis.

Patients and Methods

Patients

From May 2017 to June 2018 – after obtaining approval of the Ethics Committee (Protocol No. 23957) – 55 patients between 35 and 50 years old with menorrhagia and heavy menstrual bleeding were enrolled from the Gynecology department of Department of Surgical and Medical Sciences and Translational Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy. Twenty-eight patients were diagnosed with adenomyosis, whereas 27 patients did not meet the criteria to be diagnosed with the same pathology. All included patients had moderate or severe symptoms of dysmenorrhea and metrorrhagia. All patients were candidates for therapy with LNG-IUS due to the presence of symptoms.

Inclusion criteria were:
- no hormonal therapies in the previous six months;
- no previous diagnosis PID;
- no previous or current gynecological tumors (cervix, uterus, ovaries);
- did not undergo surgeries of the genital area.

Exclusion criteria were:
- could not be treated using LNG-IUS
- received hormonal therapies in the previous six months;
- had/ was having PID;
- had gynecological tumors (cervix, uterus, ovaries);
- underwent surgeries of the genital area;
- pregnancy.

Adenomyosis was diagnosed by an expert sonographer when at least 3 of the following signs were found at the transvaginal ultrasound (TVS):
- Increased uterine volume;
- Globulous uterine morphology;
- Uterine asymmetry;
- Alterations in the junctional zone;
- Heterogeneous myometrial texture;
- Presence of myometrial cysts;
- Hyperechogenic lines crossing the myometrium and adenomyomas.

All patients were asked for their medical history and symptoms, including menometrorrhagia, dysmenorrhea, chronic pelvic pain and dyspareunia. All patients were adequately informed and

provided written informed consent for inclusion in the study and implantation of LNG-IUS. They were also asked for providing the results of a PAP-smear and a vaginal smear done respectively within the previous year and the last month. They underwent LNG-IUS implantation between the 5th and seventh day of the menstrual cycle. Patients were divided into two cohorts, "adenomyosis" and "not-adenomyosis". Both the cohorts were followed up clinically over time and then compared to study the efficacy in the absolute value of LNG-IUS on adenomyosis.

Clinical Follow-Up

Ultrasonographic parameters and symptoms were registered before starting the treatment and during the clinical follow-up. Follow-up was conducted at 1, 3 and 6 months from the implantation. Visits were made by the same sonographer using Esaote My Class 3C equipped with a transvaginal probe of 5/7.5 MHz. In the first and third month, we used to check the correct position of the device. We revaluated with vaginal ultrasound both sonographic parameters and symptoms at month 6 when changes due to effects of the treatment would have been significantly observed. Ultrasonographic parameters were: uterine volume, uterine morphology, uterine asymmetry, alterations in the junctional zone, heterogeneous myometrial texture, presence of myometrial cysts, hyperechogenic lines crossing the myometrium and adenomyomas. Uterine volume was calculated in 3 cm using the ellipsoid formula [V = 0.5233 X (L X AP X T)]. Symptoms were: menometrorrhagia and pain (dysmenorrhea and/or dyspareunia). Menstrual blood loss was measured with the Higham score, while the pain with the visual-analogue scale (VAS).

Statistical Analysis

All data were statistically analyzed using the non-parametric Wilcoxon signed-rank test (not-continuous variables) or ANOVA 2x2x2 (continuous variables) using SPSS 24.0 (Statistical Product and Service Solution; IBM Corp., Armonk, NY, USA). Differences were considered significant at a p-value <0.05. First, a Kolmogorov-Smirnov test was made to study the distribution of data. Parametric tests and non-parametric tests were respectively conducted to investigate the variables.

Results

Our study evaluated how parameters changed in 6 months, both in each cohort and between the two cohorts. General characteristics of patients are shown in Table I. Uterine volume and menstrual blood loss resulted in having a normal distribution, while globulous uterine morphology, uterine asymmetry, junctional zone, myometrial texture, myometrial cysts, myometrial hyperechogenic lines, adenomyomas, and pain did not show a normal distribution (p<0.05). Parametric tests and non-parametric tests were respectively conducted to study the variables. ANOVA 2 (therapy: pre *vs.* post) × 2 (treatment: completed *vs.* not completed) × 2 (diagnosis: adenomyosis *vs.* other) was used to study uterine volume and menstrual blood loss. Therapy was measured within-subjects (before the implantation and after six months); treatment and diagnosis were measured between-subjects. The variable "treatment" was introduced because two patients suffering from adenomyosis and three patients not suffering from that pathology removed/eject LNG-IUS before the 6th month. This analysis shows that pre versus post-therapy changes were

Table I. General characteristics of patients.

	Adenomyosis	%	Other	%
N° patients	28		27	
Increased uterine volume	27/28	96%	24/27	89%
Globulous uterine morphology	28/28	100%	6/27	22%
Uterine asymmetry	28/28	100%	9/27	33%
Junctional zone	21/28	75%	0/27	0%
Heterogeneous myometrial texture	28/28	100%	12/27	44%
Myometrial cysts	7/28	25%	0/27	0%
Myometrial hyperechogenic lines	5/28	18%	0/27	0%
Adenomyomas	10/28	35%	0/27	0%
Menometrorrhagia	28/28	100%	27/27	100%
Pain	18/28	64%	17/27	63%

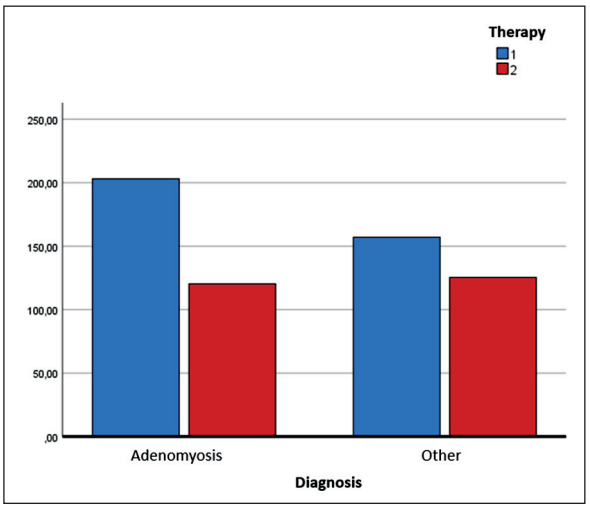

Figure 1. Analysis of uterine volume. 1: uterine volume PRE; 2: uterine volume POST.

significant in both cohorts (p=0.005). A reduction in uterine volume was observed in all patients at the 6th month (Figure 1). Moreover, the interaction between therapy and diagnosis was not significant (p=0.618).

Nevertheless, the interaction between diagnosis and treatment was significant (p=0.012), which means that the reduction in uterine volume could differ in the two cohorts if the therapy is interrupted (Table II). Treatment showed to have a significant effect on menstrual blood loss (p<0.001) (Figure 2). In the 6th month, a reduction in menstrual blood loss was observed in all patients. Moreover, the interaction between therapy and diagnosis was significant (p<0.001), which means that menstrual blood loss decreases more in adenomyosis than in other pathologies after six months. The interaction between therapy, diagnosis and treatment was also significant (p<0.001), which means that the reduction of menstrual blood loss seems to be greater in other pathologies than in adenomyosis if the treatment is interrupted (Table III). To study globulous uterine morphology, uterine asymmetry, junctional zone, myometrial texture, myometrial cysts, myometrial hyperechogenic lines, adenomyomas, and pain, were considered only patients who did not interrupt the treatment.

The non-parametric Wilcoxon signed-rank test was used to compare data collected before the treatment and at the 6th month for each variable. These analyses were conducted separately for each cohort. The analysis (Table IV) shows that all parameters improve significantly after 6 months in patients suffering from adenomyosis (asymmetry p<0.001; 3D-JZ p<0.001; myometrial texture p<0.001; myometrial cysts p=0.014; myometrial hyperechogenic lines p=0.025; adenomyomas p=0.014; pain p=0.01), except for globulous uterine morphology (p=1.000). In the control group a significant reduction of the pain was observed at the 6th month (p<0.05), whereas other parameters did not improve significantly (glob-

Table II. Uterine volume change analysis.

a Factors within-subjects	
Measure: uterine volume change	
Therapy	Dependent variable
1	Volume PRE
2	Volume POST

b Factors between-subjects		
		N
Diagnosis	Adenomyosis	28
	Other	27
Treatment	Interrupted	5
	Completed	50

c Effects test within-subjects						
Measure: association with uterine volume change						
Origin		**Sum of squares type III**	**gl**	**Quadratic mean**	**F**	**Sign.**
Therapy	Assumption of sphericity	507.923	1	5078.923	8.563	.005
Therapy * Diagnosis	Assumption of sphericity	149.501	1	149.501	.252	.618
Therapy * Treatment	Assumption of sphericity	9568.182	1	9568.182	16.131	.000
Therapy * Diagnosis * Treatment	Assumption of sphericity	399.516	1	3999.516	6.743	.012

a: Factors within-subjects; b: Factors between-subjects; c: Effects test within-subjects.

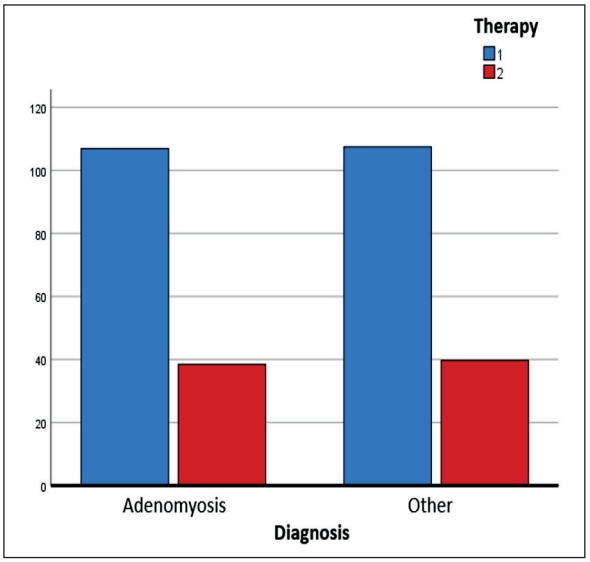

Figure 2. Analysis of menstrual blood loss 1: menstrual blood loss PRE 2: menstrual blood loss POST.

ulous uterine morphology p=1.000; asymmetry p=0.083; 3D-JZ p=1.000; myometrial texture p=1.000; myometrial cysts p=1.000; myometrial hyperechogenic lines p=1.000; adenomyomas p=1.000). As these data were non-parametric, these variables could not be analyzed between the two cohorts. Hereafter, increasing the number of patients, other types of analysis could be used to compare the two cohorts, particularly using the interpretation of variance in multilevel logistic regression. Furthermore, at the end of the study, no adverse effects were declared by the study and control groups. Furthermore, at the end of the study, no adverse effects have been declared by the study and control groups.

Discussion

This pilot study shows that LNG-IUS can treat not only symptoms of adenomyosis for which progestin releasing IUDs are used for a long time, but it may also modify ultrasonographic patterns of this pathology. Transvaginal ultrasonography plays an essential role in the diagnosis and management of adenomyosis. It is a non-invasive and cheap imaging-technique, which is globally well-accepted by patients[18]. This study represents the first step towards evaluating the correlation between LNG-IUS and consequent changes in ultrasonographic signs typical for adenomyosis. Plus, the results that we obtained are in line with those showed by Dashottar et al[19], who used MRI as a diagnostic technique. The authors of the study evaluated the same parameters at 3, 6 and 12 months from LNG-IUS implantation. They noticed a reduction of high-intensity signal in 50% of the cases and a mild reduction in the junctional zone thickness in 10% of the cases. However, they did not observe any variation of the uterine volume, which we remarkably noticed after six months from the implantation of the de-

Table III. Mestrual blood loss analysis.

a Factors within-subjects	
Measure: uterine volume change	
Therapy	Dependent variable
1	Mestrual blood loss PRE
2	Mestrual blood loss POST

b Factors between-subjects		
		N
Diagnosis	Adenomyosis	28
	Other	27
Treatment	Interrupted	5
	Completed	50

c Effects test within-subjects						
Measure: association with uterine volume change						
Origin		**Sum of squares type III**	**gl**	**Quadratic mean**	**F**	**Sign.**
Therapy	Assumption of sphericity	19769.334	1	19769.334	803.334	.000
Therapy * Diagnosis	Assumption of sphericity	318.492	1	318.492	12.942	.001
Therapy * Treatment	Assumption of sphericity	3714.534	1	3714.534	150.941	.000
Therapy * Diagnosis * Treatment	Assumption of sphericity	357.180	1	357.180	14.514	.000

a: Factors within-subjects; b: Factors between-subjects; c: Effects test within-subjects.

Table IV. Parameters after 6 months of therapy.

Diagnosis		Adenomyosis		Other	
		N	*p*	N	*p*
Morphology					
	Post	26	1.000	24	1.000
	Pre				
Asymmetry					
	Post	26	.000	24	.083
	Pre				
3D JZ					
	Post	26	.000	24	1.000
	Pre				
Texture					
	Post	26	.001	24	1.000
	Pre				
Cysts					
	Post	26	.014	24	1.000
	Pre				
Lines					
	Post	26	.025	24	1.000
	Pre				
Adenomyomas					
	Post	26	.014	24	1.000
	Pre				
Pain					
	Post	26	.001	24	.000
	Pre	26	.001	24	.000

vice (p=0.005). Reduction of the uterine volume was also observed in the cohort of patients not affected by adenomyosis, but we did not remark a significant difference in reducing the volume between the two cohorts. This result suggests that – for what concerns the volume – the effectiveness of LNG-IUS is independent of the type of diagnosis. All our cohort of patients suffering from adenomyosis that had asymmetry of the uterus at TVS showed improvements of this parameter six months from the implantation. Instead, the two patients who ejected the device before the 6th month, the asymmetry of the uterus did not improve. This finding demonstrates that a treatment that lasts less than six months does not permit to observe changes in this ultrasonographic aspect of the pathology. Moreover, in only 22% of patients not affected by adenomyosis, the asymmetry of the uterus improved, which means that – for what concerns uterine asymmetry – adenomyotic tissue has a better response to the therapy with LNG-IUS compared to other pathologies. In patients affected with other pathologies, the alteration of the junctional zone (JZ) was observed by 3D-US, whereas in 84% of patients suffering from adenomyosis, the JZ resulted better recognizable after six months of therapy with LNG-IUS. The myometrial texture improved significantly: at the beginning, 100% of women affected by adenomyosis presented marked inhomogeneous myometrial surface at TVS; after six months, in 46% of them, inhomogeneity was slight. On the contrary, in 100% of women suffering from other pathologies, the marked myometrial inhomogeneity was confirmed six months after implanting the device. As we do not know the exact nature of these pathologies, we cannot affirm that LNG-IUS is ineffective in treating myometrial features; however, we can presume that adenomyosis is more responsive to this therapy compared to other myometrial ultrasonographic abnormalities. The treatment with LNG-IUS also positively influenced the presence of myometrial cysts, hyperechogenic lines, and adenomyomas: in 100% of patients affected by adenomyosis, cysts were not detectable at the TVS 6 months after the implantation of the device, as well as hyperechogenic lines, which were regressed. In 75% of women who had adenomyosis and completed the therapy, these alterations were not detectable at the TVS the 6th month. Instead, in the two patients affected by adenomyosis who ejected the device, adenomyomas were still present at the TVs. Therefore, less than six months does not seem sufficient to

obtain the effects of the therapy on the ultrasonographic characteristics of adenomyosis. In no patients of the two cohorts, an improvement in uterine morphology was observed, which was globulous even after a six months-long therapy. Several studies evaluated the symptomatology of adenomyosis before and after the treatment with LNG-IUS, as described as follows.

Fedele et al[20] used this therapy to treat adenomyosis when associated with menorrhagia and dysmenorrhea. Barrington et al[21] reported a significant reduction of dysmenorrhea after 3 and 6 months from the beginning of the treatment, and they also noticed the resolution of menorrhagia in 90% of cases 9 months after the implantation of the device. Additionally, Sheng et al[22] used LNG-IUS to treat dysmenorrhea associated with adenomyosis, and they also observed the resolution of menorrhagia in 90% of cases 12 months after the beginning of the treatment. Our study is in line with these, and many other studies present in the literature: we confirmed the excellent efficiency of LNG-IUS in treating menorrhagia and dysmenorrhea associated not only with adenomyosis but also with different pathologies. All patients recruited in our study presented menorrhagia (Higham score > 100); in 100% of cases, we observed a significant reduction of menstrual blood flow six months after the beginning of the therapy ($p<0.001$). In the 6th month we also observed that the reduction of menstrual blood flow was more significant in patients affected by adenomyosis than in patients affected by other pathologies ($p<0.001$), probably because of more excellent responsiveness of adenomyotic tissue to the progestin therapy. In case of interrupted treatment, we noticed that the reduction in menstrual blood flow resulted lower than the reduction obtained from a six month-extended treatment, even if present. Moreover, in patients affected by adenomyosis that interrupted the treatment, the reduction of menstrual blood flow is lower compared to women suffering from other pathologies. These results may suggest that for what it may concern the menstrual blood flow, patients affected with adenomyosis have more excellent responsiveness in long-term therapy than patients affected by other pathologies. However, the number of patients is still too limited to support this hypothesis. In the end, even pain diminished a lot in both cohorts: only one patient suffering from adenomyosis had dyspareunia at the 6th month from the beginning of the therapy, and only two patients affected by other pathologies did not notice any decrease in pain. In our study, 2/28 women affected by adenomyosis (7%) and 3/27 women affected by different pathologies (11%) ejected or removed LNG-IUS before the 6th month of treatment. The most frequent reason for ejection was abundant menstrual blood flow, whereas patients who removed the device complained of irregular uterine bleeding and/or abdominal pain and/or dyspareunia. Women ejected or removed LNG-IUS before the 6th month from the implantation when the therapy did not have its maximum effect. Our study presents a few limitations: first of all, it is a not-multicentral and randomized study, plus, the number of patients is not large enough to elaborate in profound some aspects that emerged from the analysis. However, it opens the way to further investigations that could allow us to understand those aspects better. Moreover, it should be reported how other elements linked to progestin therapy were not investigated yet, for example, weight gain and/or mood swings tending to depression.

Conclusions

This study aimed to verify the efficiency of the therapy with LNG-IUS to treat menometrorrhagia and dysmenorrhea. Results we obtained are significant, showing that LNG-IUS is an effective therapy to treat typical symptoms of this pathology (menometrorrhagia, dysmenorrhea, dyspareunia) and its ultrasonographic characteristics, which underwent an essential reduction in line with symptoms. It does not prove that LNG-IUS and similar devices represent a definitive turning point in the treatment of adenomyosis. Each case has to be considered and evaluated in its entirety and complexity (age, parity and reproductive desire, quality of life and symptoms), and each therapy has to be personalized. However, we can state that LNG-IUS should be considered a valid alternative to other treatments (hormonal, symptomatic or surgical) commonly used to treat adenomyosis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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