ZKTB ORIGINAL RESEARCH

Comparison of the Levonorgestrel-Releasing Intrauterine System and Oral Tranexamic Acid in the Treatment of Dysfunctional Uterine Bleeding

Disfonksiyonel Uterin Kanama Tedavisinde Levonorgestrel Salgılayan İntrauterin Sistem ve Oral Traneksamik Asit Etkinliğinin Karşılaştırılması

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ABSTRACT

Objective: *To compare LNG-IUS and oral tranexamic acid in disfunctional uterine bleeding (DUB) therapy in terms of efficacy in reducing blood loss during menstruation, side effects, and compliance with therapy.*

Material and Methods: *60 patients who were diagnosed with DUB and were treated with either oral tranexamic acid 3gr/day or LNG-IUS were included in the study. Bleeding scores (PBAS), duration of bleeding and haemoglobin values before the therapy were recorded. Patients were evaluated again for the same parameters and possible side effects on the 3rd and 6th months of therapy.*

Results: *Decrease in duration of bleeding on the 3rd and 6th months of therapy were statistically significant in both groups (p<0,05). While there was no statistically significant difference on the decrease in the duration of bleeding on the 3rd month of therapy (p>0,05), the decrease was more significant in the LNG-IUS group than the tranexamic acid group on the 6th month (p<0,05). In the tranexamic acid group, PBAS dropped by 55 % on the 3rd month, and 62% on the 6th month, but these changes were not significantly different from each other (p>0,05). In the LNG-IUS group, PBAS decreased by 87.5 % on the 3rd month, and 90.5% on the 6th month, and these changes were statistically significant (p<0,05). However, the decrease in the amount of bleeding was significantly more in the LNG-IUS group than the tranexamic acid group (p<0,05). While haemoglobin levels increased 5.6% on the 3rd month and 9.4% on the 6th month in the LNG-IUS group, they increased 3.6% on the 3rd month and 4.5% on the 6th month in the tranexamic acid group. In the LNG-IUS group the most common complaint was mastalgia on the 3rd month of therapy (40%, 10 patients), and oligomenorrhea-amenorrhea on the 6th month (43%, 10 patients). After 6 months, 78% of patients continued the treatment, while 2 patients (6.6%) quit the therapy because of the side effects. In the tranexamic acid group, the compliance rate was 63%, and none of the patients had discontinued the therapy due to side effects.*

Conclusion: *Even though LNG-IUD is more effective than tranexamic acid in reducing blood loss in DUB patients, the major change in the menstrual cycle pattern and systemic side effects are the most common reasons for discontinuing therapy. Tranexamic acid reduces blood loss while conserving cycle patterns and fertility, and is better tolerated.*

Keywords: *disfunctional uterine bleeding, levonorgestrel-releasing intrauterine system, tranexamic acid*

ÖZET

Amaç: *Disfonksiyonel uterin kanama (DUK) tedavisinde LNG-IUS (Levonergestrel salgılayan intrauterin sistem) ve oral traneksamik asit menstrüel kan kaybını azaltmadaki etkinliği, yan etkiler ve tedaviye devam açısından karşılaştırılmıştır.*

Gereç ve Yöntemler: *Çalışmaya DUK tanısı alıp LNG-IUS uygulanan ve 3 gr/gün oral traneksamik asit kullanan toplam 60 hasta dahil edildi. Hastaların gözlemsel kanama skorlama sistemi ile hesaplanmış tedavi öncesi kanama skorları (PBAS), kanamalı gün sayıları ve hemoglobin değerleri kaydedildi. Hastalar tedavinin 3 ve 6. aylarında çağrılarak kanama skorları (PBAS), kanamalı gün sayıları, hemoglobin değerleri kaydedilip, yan etkiler açısından ayrıntılı sorgulandı.*

Bulgular: *İki gruptada 3 ve 6. ayda kanamalı gün sayısındaki azalma istatiksel olarak anlamlıdır (p<0,05). İki grup arasında kanamalı gün sayısındaki azalma açısından 3. ayda istatistiksel anlamlı farklılık yokken (p>0,05), 6. ayda LNG-IUS grubundaki azalma traneksamik asit grubundaki azalmadan daha fazladır (p<0,05). Traneksamik asit grubunda PBAS'de 3. ayda %55 azalma 6. ayda %62 azalma izlensede, bu azalmalar istatiksel olarak birbirinden farklı değildir (p>0,05). LNG-IUS grubunda PBAS'de 3. ayda %87,5 ve 6. ayda %90,5 azalma olup, 6. aydaki azalma istatiksel olarak daha fazladır (p<0,05). Ancak iki grup arasında kanama miktarındaki azalma LNG-IUS grubunda daha fazla olup bu azalma istatiksel olarakta anlamlıdır (p<0,05). LNG-IUS grubunda hemoglobin düzeyinde 3. ayda %5,6, 6. ayda %9,4 artış izlenirken, traneksamik asit grubunda 3. ayda %3,6, 6. ayda %4,5 artış izlenmiş olup, artış açısından iki grup istatiksel olarak benzerdir (p>0,05). LNG-IUS uygulanan gruptaki 3. ayın sonunda 10 (%40) hastada mastalji, 6. ayda 10 (%43) hastada oligo-amenore en sık yan etki idi. Bu grupta 6 ay sonunda tedaviye devam oranı %78 iken, 2 (%6,6) hasta yan etkiler nedeniyle tedaviyi bıraktı. Traneksamik asit grubunda 6 ay sonunda tedaviye devam oranı %63 iken hiçbir hasta yan etkiler nedeniyle tedaviyi bırakmadı.*

Sonuç: *LNG-IUS DUK tedavisinde kan kaybını azaltmada traneksamik asitten daha etkin olsada menstrüel siklus paternindeki radikal değişim ve sistemik yan etkiler tedaviyi sürdürmemenin en sık nedenidir. Traneksamik asit fertiliteyi etkilemeden, siklus paternlerini bozmadan ve daha iyi tolere edilen yan etkilerle kan kabında azalma sağlar.*

Anahtar Kelimeler: *disfonksiyonel uterin kanama, levonergestrel salan rahim içi sistem, traneksamik asit*

INTRODUCTION

Dysfunctional uterine bleeding (DUB) is the diagnosis given to patients with excessive uterine bleeding after exclusion of any demonstrable pathology. It includes both anovulatory and ovulatory heavy bleeding and accounts for 10–15% of all gynaecological complaints[1]. Although many medical and surgical treatment options are available for DUB, hysterectomy is widely used despite its accompanying morbidity. In the United States it is estimated that 4.5–40% of approximately 600,000 hysterectomies performed each year are for heavy menstrual bleeding/anovulatory bleeding. This wide range reflects the differences in such diverse factors as procedure coding and patterns of practice. Indeed, there is evidence that a large proportion of hysterectomies may be inappropriate or are at least performed without prior adequate investigation, at-

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tempts at medical therapy or consideration of less invasive surgical options [2–7].

While surgery may be a suitable option for postmenopausal women, effective and less invasive alternatives should be sought for women of reproductive age. Considering the cost and morbidity of hysterectomy, it is highly desirable to develop alternative treatment options for DUB. Oral progestogens have been the most widely used medical treatment for the last 30 years. Even though they have benefited most patients, some have reported increased bleeding. Moreover, poor patient compliance to treatment is a common occurrence, since many women do not like taking pills for a long period of time.

The aim of our study was to compare the levonorgestrel-releasing intrauterine system (LNGIUS) with oral tranexamic acid in women with DUB in terms of efficacy in reducing menstrual blood loss, side effects and compliance with therapy.

MATERIAL AND METHOD

The study was a randomised controlled trial performed over 6 months between July 2007 and July 2008 at our centre in Istanbul and comprised volunteers aged between 35 and 51 years with a diagnosis of DUB. Informed consent was obtained from all participants and the study was approved by the hospital's ethics committee. A detailed gynaecological history was taken and a complete blood count recorded. Physical and gynaecological examinations were carried out and an ultrasound evaluation was performed to rule out any pelvic pathology. Hysteroscopy was done in selected patients and endometrial biopsy in all patients. Patients with an organic pathology (fibroids, atypiaon endometrial pathology or thyroid disease), a history of medical therapy or unwillingness to accept medical therapy were excluded from the study. A basic visual technique developed by Janssen et al. [8] was used to distinguish menorrhagia from normal menstrual blood loss, comprising an illustrated form (pictorial blood loss assessment chart [PBAC]) to determine the amount of menstrual blood loss: pads are graded as lightly, moderately or heavily soiled and are given 1, 5 or 20 points, respectively; tampons are classified in a similar manner and are given 1, 5 and 10 points, respectively; 185 points is used as the cut-off value. PBAC bleeding scores were recorded prior to therapy. A total of 84 women with heavy menstrual bleeding (>185 points) were screened, 24 of whom were excluded: 12 due to fibroids, three due to atypia on endometrial pathology, two patients were hypothyroid and seven had a history of medical therapy. The patients were randomized to two groups and 30 were fitted with an LNG-IUS and 30 were treated with oral tranexamic acid. Tranexamic acid was given in a dosege of 3 g/day (1 g t.i.d.); the total daily dose did not exceed 4 g. Treatment was initiated at the onset of menstrual bleeding and continued until the bleeding stopped. If side effects occurred, the dosage was reduced to 2 g/day (1 g b.i.d.). The patients were instructed to complete the illustrated forms and after 3 and 6 months of therapy the bleeding scores, duration of bleeding and haemoglobin values were reevaluated and any side effects identified. Possible evaluated side effects of the LNG-IUS were spotting, oligomenorrhoea, amenorrhoea, lower abdominal pain, acne and other dermatological complaints, back pain, mastalgia, headache, emotional changes, nausea, hirsutism, oedema and weight gain. Amenorrhoea was defined as no menstrual period for more than 3 months. Oligomenorrhoea was defined as infrequent irregular bleeding occurring at intervals greater than 45 days. Possible evaluated side effects of tranexamic acid were headache, nausea, dizziness and abdominal pain. The results of the study were analysed using SPSS software (Statistical Package for Social Sciences) for Windows 13.0. Student's t-test was used to compare the age parameter of each group and the Mann-Whitney U-test was used to compare gravidity. The paired ANOVA test (F) and multi (double) comparisons were performed with Bonferroni correction to analyse variables in duration of bleeding, observational bleeding scores (PBAC) and haemoglobin levels. For all tests, a p-value of 0.05 was considered significant.

RESULTS

There were no statistically significant differences between the LNG-IUS (n= 30) and tranexamic acid (n= 30) groups prior to therapy: the average age of the patients was 41.9 ± 3.4 and 41.4 ± 3.1 years, respectively; average parity was 2.7 ± 1.0 and 2.9 ± 1.2, respectively; average duration of bleeding was 10.3 ± 4.1 and 9.8 ± 3.0 days, respectively; observational bleeding scores (PBAC) were 393 ± 74.2 and 402 ± 88, respectively; and haemoglobin values were 10.6 ± 1.3 and 10.9 ± 1.4 g/dl, respectively. In the first 3 months the duration of bleeding decreased significantly in the LNG-IUS group ($p<0.05$); the most common side effect was spotting.

Table I: Duration of bleeding (days; mean ± SD) at 3 and 6 months of therapy. *p < 0.05 vs. baseline; †p < 0.05 LNG-IUS vs tranexamic acid.

	LNG-IUS	Tranexamic acid
Baseline	10.3 ± 4.1	9.8 ± 3.0
3 months	7.7 ± 4.1*	6.3 ± 1.5*
6 months	2.8 ± 2.2*	5.6 ± 0.7*

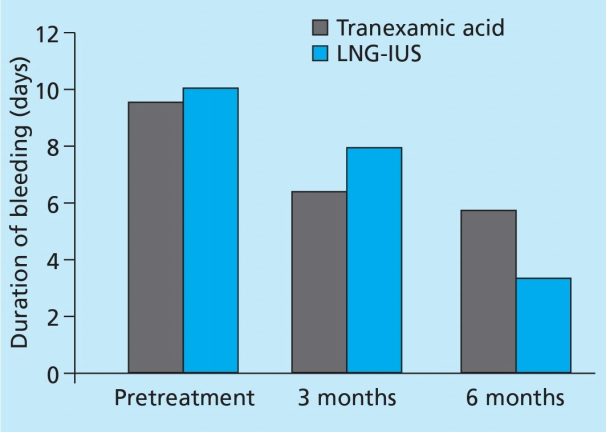

Figure 1: Comparison of the decrease in the duration of bleeding in the two treatment groups.

Between 3 and 6 months, the decrease in the duration of bleeding was also significant in this group ($p<0.05$). The duration of bleeding decreased significantly in the first 3 months in the tranexamic acid group ($p<0.05$); however, it did not decrease significantly between 3 and 6 months. At 6 months, the decrease in the duration of bleeding was significantly greater in the LNG-IUS group ($p<0.05$) than in the tranexamic acid group in comparison with baseline (Table I, Figure 1).

There was a statistically significant decrease in observational bleeding scores (PBAC) in both groups at the end of 3 and 6 months ($p<0.05$). In the tranexamic acid group, the PBAC had dropped by 55% at 3 months and by 62% at 6 months, but these changes did not differ significantly from each other. In the LNG-IUS group, the PBAC had decreased by 87.5% at 3 months and by 90.5% at 6 months and these changes were statistically significant ($p<0.05$). At 6 months, the decrease in the amount of menstrual bleeding was significantly greater in the LNG-IUS group ($p<0.05$) than in the tranexamic acid group in comparison with baseline (Table II, Figure 2).

Table II: Observational bleeding scores (PBAC; mean ± SD) at 3 and 6 months of therapy. *p < 0.05 vs. baseline; †p < 0.05 LNG-IUS vs. tranexamic acid.

	LNG-IUS	Tranexamic acid
Baseline	393.0 ± 74.3	402.7 ± 88.8
3 months	49.4 ± 37.5*†	182.1 ± 77.0*
6 months	37.8 ± 32.5*†	153.6 ± 57.2*

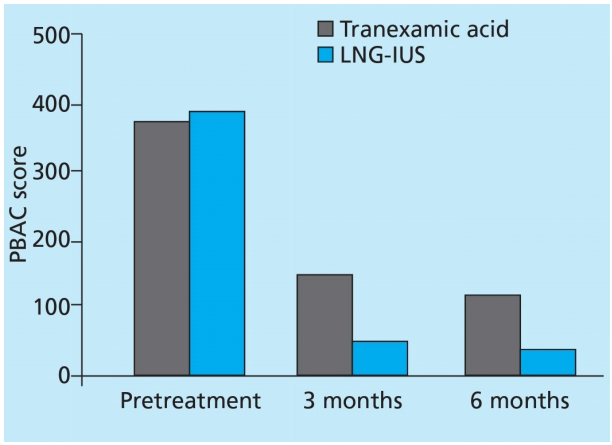

Figure 2: Comparison of the decrease in observational bleeding scores (PBAS) in the two treatment groups.

Haemoglobin levels had increased significantly at the end of 3 and 6 months in both groups (5.6% and 9.4%, respectively, in the LNG-IUS group and 3.6% and 4.5%, respectively, in the tranexamic acid group; $p<0.05$). Both increases were statistically similar (Table III, Figure 3).

Table III: Haemoglobin levels (g/dl; mean ± SD) at 3 and 6 months of therapy. *p < 0.05 vs. baseline.

	LNG-IUS	Tranexamic acid
Baseline	10.7 ± 1.3	11.0 ± 1.4
3 months	11.4 ± 1.5*	11.3 ± 1.2*
6 months	11.4 ± 1.5*	11.7 ± 1.2*

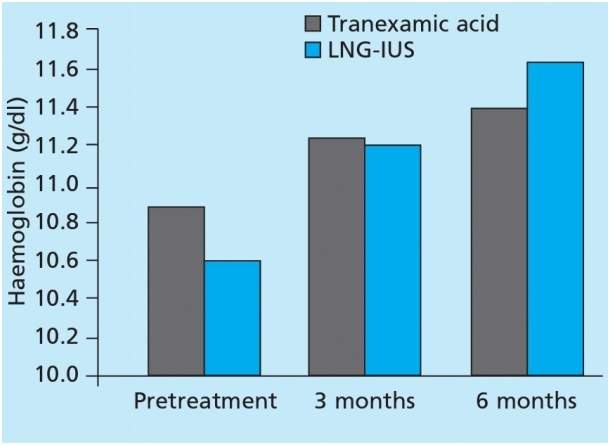

Figure 3: Comparison of the increase in haemoglobin levels in the two treatment groups.

In the LNG-IUS group, 10 patients (40%) complained of spotting at 3 months but only four patients (17.3%) at 6 months. None discontinued therapy for this complaint. Five patients (20%) had amenorrhoea or oligomenorrhoea at 3 months and 10 patients (43.4%) at 6 months. Since all patients had been informed about this possible effect before starting therapy, only one requested to have her LNG-IUS removed for this reason. In comparison with the third month, spotting decreased and oligoamenorrhoea increased significantly at 6 months ($p<0.05$). In the LNG-IUS group, functional ovarian cysts were identified in three patients (12%) at 3 months, but only one patient's cyst (4.3%) persisted into the sixth month. These cysts were less than 5 cm in diameter, simple, painless and resolved spontaneously. The most common complaint after bleeding patterns was mastalgia. In the LNG-IUS group, at the end of 3 months, five patients (20%) reported mastalgia, three (12%) reported oedema and three (12%) reported weight gain. At the end of 6 months, four patients (17.3%) reported mastalgia, three (12%) reported oedema and four (17.3%) reported weight gain. None of the patients abandoned the therapy for reasons of mastalgia, oedema or weight gain. Less common complaints in the LNG-IUS group were headache (one patient [4%] at 3 months, two patients [8%] at 6 months), hirsutism (one patient [4.3%] at 6 months) and pelvic pain (two patients [8%] at 3 months, four patients [17.3%] at 6 months). One patient discontinued therapy because of severe pelvic pain. At the end of 6 months, two patients (8.6%) had their LNG-IUS removed due to side effects.

Table IV: Side effect rates (% of patients) in the LNG-IUS group at 3 and 6 months of therapy.

	3 months	6 months
Spotting	40.0	17.3
Amenorrhoea/oligomenorrhoea	20.0	43.4
Mastalgia	20.0	17.3
Oedema	12.0	12.0
Weight gain	12.0	17.3
Headache	4.0	8.0
Pelvic pain	8.0	17.3
Hirsutism	—	4.3
Functional ovarian cysts	12.0	4.3

One patient's reason was amenorrhoea. The other could not tolerate pelvic pain. Expulsion of the LNG-IUS occurred in two patients (8%) at the end of 3 months, one partial and the other complete. No perforations, pregnancies or pelvic inflammatory disease were reported at either 3 or 6 months (Table IV).

In the oral tranexamic acid group, two patients (7.6%) complained of nausea, which had resolved at 6 months after reducing the drug dosage. In the same group, two patients (7.6%) reported abdominal pain at 3 months and one patient (5.2%) reported abdominal pain at 6 months. None considered their complaints severe enough to abandon therapy. At 3 months, one patient (3.8%) reported headache, which persisted despite a dose reduction. Although one patient (5.2%) reported diarrhoea at 6 months, it resolved the next day. No pregnancies were reported and none of the patients in the tranexamic acid group discontinued therapy because of side effects (Table V).

Table V: Side effect rates (% of patients) in the tranexamic acid group at 3 and 6 months of therapy.

	3 months	6 months
Nausea	7.6	—
Abdominal pain	7.6	5.2
Headache	3.8	5.2
Diarrhoea	—	5.2

One patient in the LNG-IUS group had a hysterectomy in the first month, after her endometrial biopsy report indicated simple endometrial hyperplasia with without atypia. Before the first routine control examination at 3 months, four patients complained of increased bleeding. On examination, two devices were found to be in the correct position; however, one patient had partial expulsion of the LNG-IUS and it was removed.

In the fourth patient, complete expulsion of the device was detected. No organic cause to explain these displacements, such as a submucous myoma or an endometrial polyp, had been detected in the manual and ultrasonographic examinations performed prior to therapy, nor in the pathological studies following hysterectomy. Whereas no pathology was detected in the routine control examinations, anaemia necessitating blood transfusion was present in one patient.

All four patients underwent hysterectomy. In the histopathological evaluation of the hysterectomy specimens only one patient was reported to have an intramural myoma, measuring 1.5 cm. Four patients in the tranexamic acid group abandoned therapy at the end of 3 months due to increased vaginal bleeding. Because they were aged below 40, an LNG-IUS was fitted in two of these patients who had no detected pathology in their routine control examination. The other two patients underwent hysterectomy and no pathology was detected in the histopathological examination of the hysterectomy specimens. Three months later, seven patients were readmitted due to an increase in the amount of bleeding. Hysteroscopic polyp excision was performed in one patient in whom an endometrial polyp was detected by saline infusion sonohysterography, performed after the discovery of an endometrial thickness of 24 mm during the routine control examination. Of the remaining six patients, three admitted that they had not taken the drug as instructed and three confirmed that they had taken the drug regularly. An LNG-IUS was fitted in three patients and a further three requested hysterectomy. While the histopathology was normal in two patients, a uterine myoma was detected in the hysterectomy material of one patient. At the end of the 6-month follow-up period, the rates of compliance with therapy were 78% in the LNG-IUS group and 63% in the tranexamic acid group ($p<0.05$). A comparison of various parameters between the LNG-IUS and tranexamic acid groups after 6 months of follow-up is given in Table VI.

Table VI: Comparison of LNG-IUS and oral tranexamic acid therapy (% change and % of patients) at 6 months vs. baseline (*$p < 0.05$).

	LNG-IUS	Tranexamic acid
Decrease in duration of bleeding (% change)	72.8*	43.8*
Decrease in observational bleeding scores (PBAS) (% change)	90.0*	62.0*
Increase in haemoglobin levels (% change)	9.4	4.5
Continuation with therapy (% of patients)	78.0	63.0
Discontinuation of therapy (% of patients) due to side effects	6.6	0.0
Hysterectomy rate(% of patients)	16.6	16.6

DISCUSSION

Patients in the reproductive and even premenopausal period tend to prefer conservative treatment modalities due to the psychosocial benefits, avoidance of surgical and anaesthesia risks, and preservation of sexual function. This has prompted the search for effective therapeutic options with few side effects and reversible contraceptive properties. Progestogens have been the most commonly prescribed drugs for the past 30 years and are still among the most common due to these factors, even though they are not highly effective. Systemic hormonal side effects occur when they are administered in higher doses to achieve a more potent effect. However, the most important problem with oral progestogen therapy is patient compliance and continuance with therapy [9,10]. Antifibrinolytic drugs such as tranexamic acid block fibrinolytic activity in the endometrium by competitively inhibiting the conversion of plasminogen to plasmin.

The efficacy of tranexamic acid in the treatment of DUB has been evaluated in many studies.

Although the recommended dose varies from one region to another, the approved dose in the European Union is 1–1.5 g, 3–4 times daily (4–4.5 g/day). In studies of tranexamic acid used in these dosages, Bonnar and Sheppard [11], Callender et al. [12], Coulter et al. [13], Milsom et al. [14] and Kriplani et al. [15] reported a 34–60% decrease in menstrual blood loss in comparison with placebo after 3 months of therapy. Similarly, in our study we also detected a 55% decrease in menstrual blood loss at 3 months and a 62% decrease at 6 months.

This effect was also apparent in the reduced number of days of bleeding, resulting in a 43.8% decrease at 6 months.

The LNG-IUS shows its effect locally by secreting 20 μg of levonorgestrel daily, causing only minimal hormonal side effects. It is currently being used for the treatment of menorrhagia in 98 countries. Many studies throughout the world have been conducted into its use and a decrease in blood loss of 86% at 3 months and 97% by the end of the first year has been reported by many clinicians [16, 17]. We were able to demonstrate the superiority of the LNG-IUS over tranexamic acid in the treatment of DUB. The decrease in menstrual blood loss in the LNG-IUS group was 87.5% at 3 months (vs. 55% in the tranexamic acid group) and 90.5% at 6 months (vs. 62% in the tranexamic acid group). The decrease in menstrual blood loss in the LNG-IUS group was significantly higher than in the tranexamic group ($p<0.05$). A 72.8% decrease in the number of days of menstrual bleeding was also observed in the LNG-IUS group (vs. 43.8% in the tranexamic acid group; $p<0.05$).

In their systematic review of LNG-IUS use, Stewart et al. [18] detected a mean rate of treatment discontinuation of 20% in randomized controlled studies and of 17% in case series. In individual studies, therapy was found to be abandoned due to side effects in 9–25% of cases. The side effects were due to the mechanical effects of the LNG-IUS or to the systemic effects of progestogen. The most frequently reported side effect in the first 3 months was spotting, which, along with displacement of the device, intermenstrual or prolonged bleeding, was one of the main reasons for abandoning therapy. It is imperative for the compliance of patients using the LNGIUS to inform them about the changes they may expect in their menstrual pattern, such as initial spotting and oligomenorrhoea. In our study, 22% of patients in the LNG-IUS group discontinued treatment at 6 months.

The incidence of side effects of tranexamic acid has been reported in the literature to be 12–33%. The side effects are dose-dependent and, when dysmenorrhoea is excluded, most are gastrointestinal effects. Decreasing the dosage and number of days of drug intake decreases the incidence of side effects [19, 20]. No study in the literature has compared the cost of the LNG-IUS with that of tranexamic acid therapy. This is because tranexamic acid is not used over a long period of time.

The ideal therapy for the treatment of DUB should be the one that has the fewest side effects, that provides the highest level of patient satisfaction and the greatest efficacy. Drug therapy is much easier to comply with when it is applied only during the menstrual period. Tranexamic acid is one of the firstline therapy options that fulfils these criteria in patients unwilling to take hormonal therapy and who do not desire contraception. Because the LNG-IUS is more costly than other therapy options, its use may be more limited.

The LNG-IUS was found to be more effective than tranexamic acid in reducing menstrual blood loss, and treatment compliance was higher with the LNG-IUS than with tranexamic acid. However, the radical changes in menstrual patterns and systemic side effects produced by its use were the most common reasons for abandoning therapy with the LNG-IUS. Tranexamic acid reduces blood loss without affecting fertility and disturbing the cycle pattern and its side effects appear to be better tolerated. However, its efficacy in reducing menstrual blood loss was clearly inferior to that of the LNG-IUS. Because of the short follow-up period of 6 months, our study was insufficient to determine the role of tranexamic acid in the longterm treatment of menorrhagia.

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