

Menstrual Bleeding Patterns and Development of Ovarian Cysts in Turkish Levonorgestrel- Releasing Intrauterine System Users

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Abstract

Objective: The levonorgestrel-releasing intrauterine system (LNG-IUS) is a long acting, safe, and reversible method that has a strong contraceptive effect. When using this method, menstrual bleeding disturbance and functional ovarian cysts are common. The objective of this study is to evaluate the relationship between using LNG-IUSs with the development of a functional ovarian cyst and bleeding disturbance in Turkish women

Material and methods: This is a prospective study including 273 Turkish women with regular menstrual cycles who had been administered LNG-IUS for contraception. We assessed their one-year follow-up results regarding bleeding patterns and functional ovarian cysts.

Results: Oligomenorrhea was the most commonly seen menstrual bleeding disorder, seen in 13.5% of all subjects. Oligomenorrhea occurred in the 4-6th months of using a LNG-IUS in 70.27% of the subjects. During the one-year follow-up, 28% of the subjects who were administered LNG-IUSs had ovarian cysts. While 36.36% of the ovarian cysts occurred within 4-6 months, 57.14% of them appeared between 7-12 months.

Conclusion: During 1-year short-term follow-up of those using LNG-IUSs, approximately one thirds of the subjects developed functional ovarian cysts and 13.5% of all complained of oligomenorrhea.

Keywords: Intrauterine device; Levonorgestrel; Functional ovarian cyst; Menstrual bleeding

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is used commonly for both contraceptive [1] and non-contraceptive indications such as the treatment of heavy menstrual bleeding or the prevention of endometrial hyperplasia during estrogen replacement therapy [2,3]. The vertical stem of this plastic T-shaped device contains 52 mgr of levonorgestrel, which is released at a daily dose of 20 µg over 5 years (q). When using an LNG-IUS, the endometrium becomes thinner, and granular atrophy and stromal decidualization occur [4]. The response of ovaries to an LNG-IUS is directly linked to serum levels of levonorgestrel. More than 50 µg of levonorgestrel is required on a daily basis to suppress ovulation, but an LNG-IUS releases only 20 µg of levonorgestrel a day [5]. As the serum level of levonorgestrel varies largely among women; the inhibition of ovulation with an LNG-IUS occurs in very few women. After an LNG-IUS insertion, anovulatory cycles are seen in 5 to 15% of women and the level of levonorgestrel in the circulation is higher within these cycles. Plasma estradiol (E2) and progesterone measurements are at a similar level to those of women who have normal ovulation [6]. These effects are mostly seen in the first year of usage and in periods when ovulatory cycles occur [7]. However, LNG-IUS is an effective treatment for heavy menstrual bleeding [8-10], changes in bleeding patterns, especially reduction of blood loss, may be a reason to remove LNG-IUS for most women who request only contraception. LNG-IUSs have effects on quality of life depending on culture influences, religious affiliations and expectations of women. In addition, the number of women removing LNG-IUS due to bleeding disturbance or oligo/amenorrhea varies to a large extent depending on the quality of consultation [11].

On the other hand, the use of LNG-IUSs can be associated with development of functional ovarian cysts [12,13]. Although, these cysts are asymptomatic, relatively small in size and may show spontaneous resolution [14], they may lead patients to unnecessary apprehension regarding the use of this method of contraception.

The objective of this study was to assess bleeding disturbances and ovarian cysts that may develop in the first year of using an LNG-IUS in Turkish women.

Materials and Methods

273 healthy parous Turkish women with regular menstrual cycles (bleeding occurred in an interval between 25-32 days and continued not more than 5 days) who were administered LNG-IUS (Mirena[®], Schering AG, Germany) for contraception in Tepecik Training and Research Hospital, Obstetrics and Gynecology Department were included in the present study. Personal consultation was given to all subjects, who met the contraceptive conformity criteria of the World Health Organization before administering LNG-IUS. All of the subjects were assessed with vaginal ultrasonography (LogiqP5, General Electronic Co., USA) together with pelvic examination before the process. Any pathologies of the ovaries and uterus, having menstrual bleeding disturbances before LNG-IUS insertion and dislocation of intrauterine device during follow-up were exclusion criterias. The subjects' ages, number of children and miscarriages and their fertility targets were recorded. During the one year follow-up, every month, they were performed vaginal ultrasonography within 5 days of menstrual onset or within 5 days of expected menstrual onset by the same gynecologist. Also, they were questioned monthly about changes in their menstrual

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cycles. Each woman was asked to record the length of menstrual cycles, days of bleeding and self-assessment of the amount of the menstrual loss. The type of bleeding disturbance they had and in what month of use this occurred, the time of occurrence and diameters of ovarian cysts that were observed with vaginal ultrasonography during the follow-up were all noted.; Oligomenorrhea was defined as the presence of scanty bleeding in an interval longer than 6 weeks; spotting as occasional and unpredictable discharge of small amounts of blood; menorrhagia as heavy and frequent bleeding [15,16]. An ovarian cyst was defined as having a mean diameter over 25 mm [17].

We divided patients into groups according to the existence of oligomenorrhea or not; or development of ovarian cyst or not. Then, according to the beginning time of the complaint, the patients who had oligomenorrhea were divided into three subgroups. Group 1 included the patients who had oligomenorrhea within 3 months after LNG-IUS insertion; group 2 included patients who had oligomenorrhea within 4-6 months after insertion, and group 3 included the patients who had oligomenorrhea within 7-12 months after insertion. Similarly, the patients who developed ovarian cysts during 1 year follow-up were divided into three subgroups according to the beginning time of this complaint.

Each woman was informed about the study, and provided their written approval. Also, the study was approved by the Ethics Committee of the hospital.

The statistical analysis was performed using the Statistical Package for the Social Sciences version 14 (SPSS Inc., Chicago, IL, USA). Chi-squared test was used to analyze the differences within the groups. Pearson's chi-squared test was used to analyze independent non-parametric values. Significance was set at $p < 0.05$.

Results

The socio-demographical characteristics of the subjects were shown in Table 1.

During their one year follow-up, 13.5% of the subjects (n=37) were seen to have bleeding disturbances in the form of oligomenorrhea, 5% (n=18) in the form of menorrhagia and 5% (n=18) in the form of spotting.

Oligomenorrhea, the most common menstrual disorder in LNG-IUS users, was observed in only two (7%) of the 27 subjects who were older than 45 years. It was seen in 4 (9%) of the 46 subjects in the 40-44 age group, in 13 (15%) of the 88 subjects in the 35-39 age group, in 14 (17%) of the 82 subjects in the 30-34 age group, in 3 (12%) of the 25 subjects in the 25-29 age group and in one (20%) of the 5 subjects in the 19-24 age group, respectively (Table 2). There was no significant difference between age and development of oligomenorrhea ($p=0.699$). Oligomenorrhea occurred within 4-6 months of LNG-IUS insertion in 70.3% of the subjects, within the first three months of insertion in 18.9% of them and within 7-12 months of insertion in 10.8% of them. We found the difference among these subgroups significant ($p=0.000$) (Table 3).

In addition, ovarian cysts were found in 28% (n=77) of all subjects within a year. Among these patients who developed ovarian cysts during the follow-up, 35% of them (n=27) had a diameter between 51 and 60 mm. Overall, 21% (n=16) of the ovarian cysts had a diameter of 25-30 mm, 25% (n=19) were 31-40 mm, 17% (n=13) were 41-50 mm and 1.3% (n=1) were larger than 60 mm, respectively. No ovarian cyst was found in the group below 30 years of age. Ovarian cysts were found in 23 of the 27 subjects above 45 years of age, in 21 of the 46 subjects

between 40 and 44 years of age, in 18 of the 88 subjects between 35 and 39 years of age, and in 15 of the 82 subjects between 30 and 34 years of age (Table 2). As the ages of subjects decreased, the percentage of ovarian cysts also decreased and this was statistically significant ($p=0.000$). 57% of the ovarian cysts occurred within 7-12 months after the administration of LNG-IUSs during one-year follow-up. Overall, 36% of the ovarian cysts occurred within 4 to 6 months of administering LNG-IUSs and 7% of them within 3 months. The differences between these three subgroups were also significant ($p=0.006$) (Table 3).

Discussion

Women using LNG-IUS experience changes in bleeding patterns such as spotting, menorrhagia and oligomenorrhea. The rate of bleeding disturbance (15-71%) varied between studies [18-20]. Oligo/amenorrhea was reported in 15-20% of the LNG-IUS users within the first year of use and increased to 30-40% with longer duration of use [15,21]. Besides, Hidalgo and et al. also observed spotting in 25% of the users at 6 months [15]. Similarly, Suvisaari and Lahteenmaki reported that spotting occurred frequently in the first 4-6 cycles after LNG-IUS insertion. However, after this transition period, regular menstrual cycles started to be seen with a decreasing number of days and amount of bleeding [22]. The present study was consistent with the literature.

There is a growing evidence of women's dissatisfaction with LNG-IUS because of a high incidence of adverse effects. Menstrual bleeding disturbance is one of the most important reason for removal of the LNG-IUS [18,23]. Where the LNG-IUS is used as a contraceptive method, reduction of blood loss is mostly considered as an advantage [24], however it may also be a reason for removal [25]. LNG-IUS

	n	%
Age(years)		
19-24	5	1.8
25-29	25	9.2
30-34	82	30
35-39	88	32.2
40-44	46	16.9
≥45	27	9.9
The number of the children		
0	0	0
1	16	5.9
2	212	77.7
3	25	9.1
≥4	20	7.3
Fertility goals		
No more wish to have a baby	212	77.6
Wish to have a baby in following 2 years	8	3
Wish to have a baby after 2 years	11	4
Uncertain	42	15.3

Table 1: Socio-demographic characteristics of the patients.

Age (years)	Oligomenorrhea		Functional ovarian Cyst	
	n	%	n	%
19-24	1	2.7	0	0
25-29	3	8.2	0	0
30-34	14	37.8	15	18.29
35-39	13	35.1	18	20.45
40-44	4	10.8	21	45.65
45 - ↑	2	5.4	23	85.18

Table 2: Distribution of oligomenorrhea and ovarian cyst occurrence in Turkish LNG-IUS users according to age.

Time	Oligomenorrhea		Functional ovarian Cyst	
	n	%	n	%
≤3 months	7	18.9	5	6.5
4-6 months	26	70.3	28	36.4
7-12 months	4	10.8	44	57.1

Table 3: Reconition time of oligomenorrhea and ovarian cysts in Turkish LNG-IUS users.

were found to be significantly more likely to discontinue because of oligomenorrhea than nonhormonal intrauterine device users [26]. In a study, it was reported that oligomenorrhea was more likely to be seen at 12 months of insertion in women who used LNG-IUS for contraception than women who used it to manage heavy menstrual bleeding [16].

Use of a LNG-IUS can be associated with the development of functional ovarian cysts [17]. In the present study, we found ovarian cysts in 28% of all subjects within a year. 57% of these occurred at 4-6months and 36% at 7-12 months after insertion. We observed that these cysts were more frequent in older women than in younger ones. Supporting our findings, the incidence of persistent ovarian follicles during LNG-IUS use has been reported in the range of 8%-31% in a study [14]. However, Borgfeldt et al. found ovarian cysts at a rate of 6.6% in a randomly sampled population of women between 25 and 40 years of age. Also, they stressed that ovarian follicles could rarely reach a diameter of 30 mm and the upper limit was not known. They observed that 82% of the cysts disappeared within a period of three months [17]. In a Finnish trial of women referred for hysterectomy or LNG-IUS due to heavy menstrual bleeding, ovarian cysts were more common among women randomized to LNG-IUS compared to hysterectomy: 17.5 vs 3.0% and 21.5 vs 8.0% at 6 and 12 months, respectively. They also reported spontaneous resolution in 94.1% of the cysts. They revealed that the occurrence of cysts did not correlate to the age or the FSH level. However, they found a weak correlation between the occurrence of cysts and irregular bleeding [13]. On the other hand, LNG-IUS use was reported to be associated with the development of ovarian cysts in 40.5% of premenopausal women at 6 months of insertion [26]. Barbosa et al. reported that LNG-IUSs sometimes inhibited ovulation and the changes in hypothalamic-pituitary- ovarian functions affected follicle development and rupture, and caused the production of new cysts [27]. In another study, an increase in the "mean arterial pulsatility index", a decrease in serum progesterone level, thinning of the endometrium and ovarian cysts were found in 31% of the subjects after a three-month treatment with LNG-IUS. All of these cysts disappeared in the four-month follow-up period. The mean serum estradiol ratios were found to be higher in the subjects who were found to have ovarian cysts than in those who did not have them. The mean serum levonorgestrel levels also tended to be higher in those subjects who were found to have ovarian cysts [28].

Ovarian cysts are also seen in women using other contraceptive methods. The presence of ovarian cysts and similarly high spontaneous resolution rates have been documented in both LNG-IUS and progestin-releasing implant users [29,30]. However, cysts were found more frequent in women using LNG-IUS than in women using combined oral contraceptives or no hormonal contraception [17].

The Royal College of Obstetricians and Gynecologists (RCOG) has stated that although there are guidelines about the management of ovarian cysts in postmenopausal women, there is no nationally accepted algorithm about the management of ovarian cysts in premenopausal women. Moreover, there is no consensus about the routine ultrasonographic follow-up of LNG- IUS users, because

ovarian cysts will be subject to spontaneous resolution at a high rate. It is not known for certain how long one should wait for the resolution of ovarian cysts and when and how often ultrasonography will be used. This issue was not raised in the past when LNG-IUS use was less common. Today, as the use of LNG-IUSs becomes more widespread, the algorithms related to ovarian cysts and their managements will gain priority [31].

There are some limitations of this study. Firstly, our sample size was small. Secondly, in our study, the evaluation of blood loss was subjective. Also, self-reported bleeding patterns could be biased that women may have been effected by their own ideas or religious affiliations or cultural influences regarding menstrual patterns. Using bleeding charts to investigate the bleeding patterns would have been objective.

Contrary to the studies concerning menstrual disturbance and ovarian cyst related to LNG-IUS in different ethnic populations, data on this topic in Turkish women is insufficient. Our study has some differences from the similar ones in the literature. For example, each ultrasonographic examination was done by the same gynecologist and was timed to a particular menstrual cycle phase. All of these methodological factors are likely to effect the results.

In conclusion, use of LNG-IUS appears to bring about some disturbance in ovarian function, resulting cyst formation and it probably exerts a local effect on endometrium, leading menstrual bleeding disturbances in Turkish women, similar to women from different nations. As Sturridge and Guillebaud stated before, the only undesired non-contraceptive effect of the LNG-IUS is possible development of functional ovarian cysts and the relationship between the level of menstrual bleeding and ovarian function; when we understand these better, we can offer appropriate consultation to women and in this way the acceptability of the method becomes maximum and we can establish continuity in the use of the method" [32].

Conflict of Interest: Umit Nayki, Cenk Nayki, Pasa Ulugi Mehmet Kulhan, Aysegul Erdonmez, Keana Ertopce and Yusuf Yildirim stated no conflict of interest.

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