Comparison of effects of levonorgestrel-releasing intrauterine devices and Cu-T 380A intrauterine devices on ovarian functions

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ABSTRACT

Our aim was to compare the effects of levonorgestrel-releasing intrauterine devices (LNG-IUD) and Cu-T380 A IUDs on ovarian functions. We included 73 volunteer women aged between 20 and 35 who attended Kahramanmaras Sutcu Imam University Gynecology and Obstetrics Policlinic for contraception requests, as well as a control group of 22 volunteer women aged between 20 and 35 who attended the clinic and had regular menstrual cycles and no gynecologic problems. The cases were separated into two groups: 38 patients with LNG-IUD inserted and 35 patients with Cu-T380 A IUD inserted. The patients were invited for controls on the 10th, 12th, 14th, and 21st days of their cycles in the first, second, and third months after IUD insertion. In the control visits, follicular development, follicle-stimulating hormone, luteinizing hormone, oestrogen and progesterone levels were measured. During the three monthly follow-ups of all patients, there were significant differences between ovarian function types (p=0.03). D type ovarian reaction rate was significantly lower in the LNG-IUD group (11.5% vs. 19.0%, p<0.05) and maximal size of follicles were significantly lower in the group using the LNG-IUD (p<0.05).The LNG-IUD was found to have an inhibitory effect on ovulation, which seems to increase its contraceptive effect.

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1. Introduction

Intrauterine devices (IUDs) are the most commonly used contraceptive methods around the world (Barbosa et al., 1990 ; Akin, 2008). There are three types of IUDs in use today: inert IUDs, copper-bearing IUDs, and hormone-releasing IUDs. The IUDs have different acting mechanisms to prevent pregnancy. Copper-bearing IUDs cause an inflammatory reaction on the endometrium, which provides not only phagocytosis of spermatozoa, but also a spermicidal affect (Brenner and Mishell, 1975; Barbosa et al., 1995). In addition, copper is thought to prevent the effect of oestrogen on the endometrium and sperm motility. The effects of copper-bearing IUDs on ovarian function and gonadotropins have been investigated by human and animal studies, and no effect on the hypothalamic-pituitary axis was found (Critchley et al., 1998; Ecochard et al., 2000).

Hormone-releasing IUDs have been used worldwide since 1976, and they offer both advantages and disadvantages in contraception. Besides contraception, levonorgestrel-releasing IUDs (LNG-IUD, Mirena) have a wide application area, including menorrhagia, endometriosis, hormone replacement therapy, leiomyoma, adenomyosis, endometrial hyperplasia, and cancer (Fortergill et al., 1982; Grewal and Burkman, 2003). The acting mechanisms of the LNG-IUD can be classified by the affected location: cervical, endometrial, and ovarian. The LNG-IUD makes cervical mucus more viscous and inhibits proliferation of the endometrium (Lahteenmaki et al., 1991; Jarvela et al., 1998; Guillebaud, 2003). The effects of the LNG-IUD on ovarian function are identified as four types: anovulation with a decrease in oestrogen production, anovulation with increasing in oestrogen production, luteal phase failure, and normal ovulation. The first and

second types of effects occur in high plasma concentrations of levonorgestrel (Landren and Diczfaluzy, 1980). However, the inhibition of ovulation is thought to be ineffective in contraception, because of the ineffective dose of levonorgestrel. The studies about the effects of the LNG-IUD on ovarian function have indicated different results. While some studies have found suppression on ovulation and inhibition on the hypothalamic-pituitary axis, some have mentioned that there was no significant effect on ovarian functions (Landren and Diczfaluzy, 1980; Leader et al., 1985; Lenz, 1985; Luukkainen et al., 1990).

To investigate the effects of the LNG-IUD and copper-bearing IUDs on ovarian function, direct and indirect methods can be used (Marou et al., 2001). The direct method includes ultrasonographic evaluation, through which the following findings have been made at the time of ovulation: a sudden decrease in the measurement of the diameter of follicles or loss of follicles (Marou et al., 2001), the existence of the cumulus oophorus or transforming to the corpus luteum (Nelson, 2000), and free fluid in the Pouch of Douglas (Nilsson et al., 1984). However, none of these findings are specific for ovulation. Indirect methods include basal body temperature measurement, evaluation of oestrogen and luteinizing hormone, cervical mucus characteristics, measurement of mid-luteal phase progesterone, and endometrial biopsy (Marou et al., 2001).

The aim of this study was to compare the effects of LNG-IUDs and copper-bearing IUDs on ovarian function.

2. Material and methods

The study included 73, 20- to 35-year-old women with normal menstrual cycles who attended the family planning policlinic for contraception as the study group and 22,20- to 35-year-old healthy women with regular menstrual cycles and no gynaecological diseases as the control group. Women who were pregnant or nulliparous, or who had a history of pelvic inflammatory disease, ectopic pregnancy, uterine anomaly, unexplained vaginal bleeding, endocrine system disease, or drug usage were not included.

After obtaining written informed consent from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki", the study was approved by the institutional ethic committee. Gynecologic examinations, transvaginal ultrasonography (TV-USG), and conventional cervical smears were performed. The study group was divided into two groups: 35 patients with copper T 380 A IUDs (Cu-T 380) and 38 patients with LNG-IUDs. After control of the placement of the IUDs, the patients were sent home and called back on the 10th, 12th, 14th, and 21st days of their cycles in the first, second, and third months after insertion.

The patients were evaluated for ovulation on the 10th, 12th, and 14th days of their cycles in the first, second, and third months after insertion of the IUDs by transvaginal ultrasonography and measurement of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and oestrogen (E2) levels on the 12th days and progesterone levels on the 21st days of their cycles. Using transvaginal ultrasonography, ovulation was evaluated by a decrease in follicle diameter of more than

50%, loss of eco negative follicles, and presence of free fluid in the Pouch of Douglas. On the 21st day, or seven days before the expected menstruation time, serum progesterone levels were measured. The Landgren-Diczfaluzy classification was used for evaluation of ovulation: (Phillip et al., 2007)

Type A ovarian reaction: Low oestrogen and progesterone, anovulation

Type B ovarian reaction: High oestrogen, low progesterone, anovulation

Type C ovarian reaction: Normal oestrogen, low progesterone, luteal phase failure

Type D ovarian reaction: Normal oestrogen and progesterone, ovulation

A chi-square test, Fisher's Exact test, and Kruskal-Wallis variance analysis were used for statistical analysis. The Mann-Whitney U test was used as a post hoc test. In all tests, $p < 0.05$ was accepted as statistically significant.

3. Results

The study group included 73 subjects and the control group included 22 subjects. One patient who planned to have an LNG-IUD inserted was diagnosed with uterus bicornis; one patient had a result of atypical squamous cells of undetermined significance (ASC-US); and seven patients with LNG-IUDs and five patients with Cu-T380A IUDs could not be contacted. Therefore, the study was completed with 57 patients. The demographic characteristics of the groups are shown in Table 1.

Table 1. Demographic characteristics of the groups

	Cu-T380A-IUD (n=28)	LNG-IUD (n=29)	Control (n=22)	p
Age (year)	28.2±3.4	33.2±2.4	31.1±4.1	0.00
BMI (kg/m²)	27.7±3.7	28.8±6.1	25.0±3.3	0.01
Gravida	3.1±1.1	2.9±0.9	2.3±1.8	0.15
Parity	2.9±1.0	2.7±0.9	2.0±1.5	0.06

Cu-T380-IUD; Copper-releasing intrauterine device, LNG-IUD; Levonorgestrel-releasing intrauterine device, BMI; Body mass index

The maximum follicle diameter measurements by transvaginal ultrasonography on the 10th, 12th, and 14th days in the first, second, and third months after insertion of the IUDs are shown in Table 2.

Table 2. Maximum follicular diameter measurements by TV-USG

	Cu-T380A-IUD (n=28)	LNG-IUD (n=29)	Control (n=22)	p
Maximum follicle diameter (First month)	12.3±5.9	11.6±8.7	12.9±5.3	0.2
Maximum follicle diameter (Second month)	12.2±5.4	9.2±9.1	12.9±5.3	0.00
Maximum follicle diameter (Third month)	1.6±5.7	9.5±8.9	12.9±5.3	0.00

Cu-T380-IUD; Copper-releasing intrauterine device, LNG-IUD; Levonorgestrel-releasing intrauterine device.

The study group with LNG-IUD had statistically significant weak follicle development (p<0.05) in the second and third months after insertion compared to the Cu T 380 A IUD and control groups.

The ratio of follicle development and rupture by TV-USG are shown in Table 3.

Table 3. The ratio of follicle development and rupture in all groups

Ratio %	Cu-T380A-IUD (n=28)	LNG-IUD (n=29)	Control (n=22)	p
Follicle development				
First month	64%	55%	72%	0.43
Second month	67%	31%	72%	0.00
Third month	60%	41%	72%	0.07
Follicle rupture				
First month	21%	6%	22%	0.21
Second month	17%	10%	22%	0.48
Third month)	21%	10%	22%	0.42

Cu-T380-IUD; Copper-releasing intrauterine device, LNG-IUD; Levonorgestrel-releasing intrauterine device

There was a statistically significant decrease in the follicle development of the group with the LNG-IUD (p<0.05). However, the ratio of follicle rupture did not show any difference in any of the groups.

The evaluation of FSH, LH, oestrogen, and progesterone levels are shown in Table 4.

The level of progesterone in the LNG-IUD group was statistically significantly low after two months of insertion, the level of FSH was significantly high, and E2 was lower (p<0.05).

Table 4. FSH, LH, and oestrogen levels on the 12th days of subjects' cycles and progesterone levels on the 21st day of subjects' cycles after IUD insertion

	Cu-T380A-IUD (n=28)	LNG-IUD (n=29)	Control (n=22)	p
Progesterone (ng/ml)				
1st month	5.3±6.0	2.4±3.7	5.0±4.9	0.02
2 nd month	4.1±4.2	2.0±3.6	5.0±4.9	0.02
3 rd month	4.7±4.5	3.2±4.2	5.0±4.9	0.31
FSH (mIU/ml)				
1st month	4.2±2.6	4.6±2.8	4.4±2.7	0.91
2 nd month	4.8±2.5	5.6±2.9	4.4±2.7	0.18
3 rd month	4.4±2.0	5.9±3.3	4.4±2.7	0.04
LH (mIU/ml)				
1st month	6.7±5.3	5.1±3.6	5.5±4.3	0.22
2 nd month	5.8±3.4	5.0±2.8	5.5±4.3	0.65
3 rd month	4.7±3.4	5.7±3.8	5.5±4.3	0.62
E2 (pg/ml)				
1st month	113.8±69.3	118.8±67.3	113.1±73.1	0.37
2 nd month	128.7±64.4	90.6±53.8	135.1±73.0	0.02
3 rd month	111.9±48.0	100.9±45.3	135.1±73.0	0.14

FSH; Follicle stimulating hormone, LH; Luteinizing hormone, E2; oestrogen; Cu-T380A-IUD; Copper-releasing intrauterine device, LNG-IUD; Levonorgestrel-releasing intrauterine device

The types of ovarian function seen in three groups after follow-up for three months are shown in Table 5.

When all the cycles were observed, there were statistically significant differences between all groups in the types of ovarian function (p<0.05). The ratio of D type ovarian function was significantly lower in the LNG-IUD group compared to the Cu-T380 A IUD patients (p<0.05).

Table 5. The ratio of types of ovarian function

Landgren-Diczfaluzy classification	Cu-T380A-IUD	LNG-IUD	Control
Ovarian function			
A type	35%	56%	27%
B type	23%	23%	31%
C type	21%	9%	18%
D type	19%	11%	22%

Cu-T380-IUD; Copper-releasing intrauterine device, LNG-IUD; Levonorgestrel-releasing intrauterine device

4. Discussion

In our study, we found that the LNG-IUD had an inhibitory effect on ovulation in the first two months, after which there was no significant difference from the control group. However, the Cu T380 A IUD had no significant effect on ovulation. In two different studies, Luukkainen et al. (1990) and Guillebaund et al. (2003) showed 85% ovulation in cycles after one year of insertion of LNG-IUD.

Barbosa et al. (1990) followed up with patients using LNG-IUDs for more than four years and found 88% ovulation in cycles, but only 53% follicle growth and rupture. Supporting this result, in another study, Barbosa et al. (1995) found 93% ovulation in cycles in patients using LNG-IUDs for seven years, but only 58% normal follicle development and rupture.

In our study, there was a significant decrease in follicle development with the LNG-IUD, but the Cu-T380A IUD had no significant effect on follicle development or rupture. Xiao et al. (1990) followed up with 29 cycles for one year after insertion of LNG-IUDs by measuring levels of LH and E2 on the 12th days and progesterone on the 21st day of the cycles. They found 55% anovulation, but they did not confirm this by imaging. We observed ovulation by TV-USG and measured FSH, LH, E2 and progesterone levels, and found 11.5% ovulation with the LNG-IUD.

The progesterone level on the 21st day of the cycle indicates ovulation above 2-5 ng/ml, differentiating according to studies. We found a significant decrease in levels of progesterone in the LNG-IUD group compared with the Cu-T380 A IUD and control groups, (p<0.05). The same results were shown in the studies of Jarvela et al. (1998) and Nilsson et al. (1984). While progesterone levels were lower in the LNG-IUD group in the study of Jarvela et al. (1998), the luteal phase was long and progesterone levels were low in the LNG-IUD group in the study of Nilsson et al. (1984).

Studies on the effects of copper-bearing IUDs are limited, and the results often indicate no significant effect on the hypothalamic-pituitary axis. Brenner and Mishell (1975) followed up with patients with copper-bearing IUDs for one year and

found no statistically significant effect on follicle development, rupture, or corpus luteum formation, or FSH, LH, E2, or progesterone levels. Supporting this study, we found no significant effect on ovarian function in the Cu-T380 A IUD group.

Besides the human studies on IUDs, an animal study by Turin et al. (1997) showed inhibitory effects of copper-bearing IUDs on the ovarian function and pregnancy rate of heifers. They measured progesterone on the 1st, 2nd, 20th, and 120th days of the animals' cycles and found significantly lower failure in ovulation and corpus luteum formation when compared to a control group. The copper-bearing IUD was found to be 100% effective in preventing pregnancy.

In conclusion, when we compared the effects of the LNG-IUD and the Cu T380 A IUD on ovarian function, the LNG-IUD was seen to have an inhibitory effect on ovulation just after insertion, after which there were no significant differences from the control groups. The decrease in progesterone and oestrogen and increase in FSH levels also support the inhibition on follicle development and rupture. However, the Cu T380 A IUD seemed to have no significant effect on ovarian function; therefore, this mechanism had no importance on the contraception effect, while the LNG-IUD had not only endometrial and cervical effects, but also ovarian inhibition as its acting mechanisms.

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