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Metabolic Changes in Women Using Levonorgestrel Releasing Intrauterine System

Mohamed Abdallah Rezk[1], Alaa Masoud AbdElgayed[1], Shimaa Adel Abdelsalam Allam[2], Dalia Ibrahim Mohamed Morsi[1], Heba Maged Abo shady[1]

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Menoufia University, Egypt

[2]Resident of Family planning department, Sadat City Hospital, Menoufia, Egypt

***Corresponding author:** Shimaa Adel Abdelsalam Allam, **Mobile:** (+20) 0106 420 0726, **Email:** i_wz_u89@yahoo.com

ABSTRACT

Background: The effect of levonorgestrel-releasing intrauterine system (LNG IUS) on metabolic parameters like body mass index, body weight, blood pressure, blood sugar, lipid profile and liver function test is still unclear.

Objective: To assess the possible metabolic effects of the levonorgestrel intrauterine system on serum lipids, body weight and fasting blood glucose level after a period of six months.

Subjects and Methods: A prospective study comprised 50 women attended to the Department of Family Planning in Sadat city Hospital and request intrauterine hormonal contraception during the period from December 2018 to August 2019. Full history, routine, physical examination and special investigations were taking.

Results: There were no statistically significant differences between the studied patients regarding Socio-demographic characteristics before and after 6 months follow up. Menstrual change was the most adverse effects among the studied patients (15 cases, 32.61%), followed by spotting in 6 cases (13.04%) then lower abdominal pain in 5 cases (10.87%). While, weight gain recorded the lowest frequent (2.17%). Regarding overall satisfaction with the method, most of the studied patients had very or somewhat satisfied (32 cases, 69.57%) and 14 cases (30.43%) had neutral or somewhat not satisfied.

C**onclusions:** Among the Egyptian the LNG-IUS does not have any adverse effects on metabolic parameters, TGs, LDL and blood sugar levels. Most of the studied patients had very or somewhat satisfied with methods and 30.43% had neutral or somewhat not satisfied.

Keywords: Body mass index, Intrauterine system, Levonorgestrel, Lipid profile, Metabolic changes.

INTRODUCTION

Development of progestogen-medicated IUDs started in the 1970s and approved first in Finland in 1990 of an IUD with a 52-mg levonorgestrel load initially releasing 20 microg daily (Levonova®) with a 5-year effective lifespan. The US FDA approved the 5-year 52-mg LNG-medicated IUD (Mirena®) in 2000. In 2013, FDA approved an IUD with 13.5-mg LNG (Skyla® or Jaydess®) and, in 2015, a new 52-mg LNG-IUD (Liletta®). At present, these two new 13.5- and 52-mg LNG-IUDs both have an approved lifespan of 3 years [(1)]. The levonorgestrel-releasing intrauterine system (LNG IUS) provides a long-acting, highly effective, and reversible form of contraception, with a pearl index of 0.18 per 100 women-years. The locally released hormone leads to endometrial concentrations that are 200–800 times those found after daily oral use and a plasma level that is lower than that with other forms of levonorgestrel-containing contraception [(2)].

Apart from being a reliable contraception, Mirena is now widely indicated for its non-contraceptive benefits which include treatment of menorrhagia, dysmenorrhea, premenstrual symptoms, fibroids, adenomyosis, endometriosis etc… [(3)]. Although the mechanism of action of the LNG-IUS is primarily local, the levonorgestrel that is released within the uterus is swiftly absorbed into the systemic circulation [(4)]. During the first year of use, the LNG IUS releases 20 µg of levonorgestrel every 24 hours, declining slowly over the labeled lifetime of the device. Release of the hormone decreases to 11 µg per 24 hours by the end of 5 years, with an average release rate of 14 µg per day over the life of the device [(5)]. Maximum plasma levels are reached within a few hours after LNG-IUS insertion and plateau at 150 to 200 pg/mL (0.4 to 0.6 nmol/L) within the first few weeks. This is in contrast to the much higher plasma hormone levels of combined oral contraceptives, progesterone only pills and Norplant· Plasma LNG levels from the LNG-IUS remain quite stable over time, but there is marked variation between individuals [(4)].

The side effects, which can lead to treatment discontinuation, are mainly due to the progesterone in the LNG IUS. Include unscheduled breakthrough bleeding/spotting during the initial 3 to 6 months, amenorrhea, steroidal side effects, acne, chloasma, weight change, and depression [(6)].

The gross cumulative termination rate at 5 years because of change of weight was 1.5 in users of the LNG IUS and 0 for copper-IUD. The higher gross rate of removals for weight change in users of LNG IUS most probably reflects the suspicion that the hormone was responsible for the weight gain [(7)].

Therefore, the aim of this study was to assess the possible metabolic effects of the levonorgestrel intrauterine system on serum lipids, body weight, and fasting blood glucose level after a period of six months.

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PATIENTS AND METHODS

A prospective study comprised 50 women attended to the Department of Family Planning in Sadat city Hospital and requesting intrauterine hormonal contraception during the period from December 2018 to August 2019.

Ethical consideration:

The study was approved by the Ethical Committee of Menoufia Faculty of Medicine and Sadat City General Hospital. An informed consent was obtained from all subject's guardian before the study was commenced.

Inclusion Criteria: Non-Pregnant women and woman who had at least one child. (World Health Organization. Improving Access to Quality Care in Family Planning Medical Eligibility Criteria for Contraceptive Use. 3rd ed. Geneva: WHO; 2004).

Exclusion Criteria:

Uterine anomaly: congenital or acquired including fibroids if they distort the uterine cavity, presence or suspected PID or history of PID unless there has been a subsequent intrauterine pregnancy, patients with unexplained uterine bleeding, known or suspected uterine or cervical cancer, known or suspected breast cancer or other progestin-sensitive cancer now or in the past, liver disease or liver tumor, untreated acute cervicitis or vaginitis until infection is controlled, hypersensitivity to any component of this product, diabetic or hypertensive patients or having a disease of dyslipidemia or hyperlipidemia and BMI > 25.

All women included in the study were subjected to the following before LNG-IUS insertion:

Full history taking: e.g. age, residence, consanguinity, splenectomy and consanguinity, education, history of illness, residence, drug taking …etc.

Clinical examination: e.g. body weight, height, waist circumference (WC) systolic and diastolic blood pressure measurements. WC was taken midway between the lowest rib margin and the iliac crest.

Laboratory testing: following overnight fast 8-14 hours, baseline investigation in the form of fasting blood glucose (FBG) using Sysmex KX-21 automatized hematology analyzer (Sysmex corporation, Japan) and fasting blood lipid profile, serum concentration of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) using the open system autoanalyzer synchron CX5 (Beckman, USA).

After insertion LNG-IUS: Follow up in the Outpatient Clinic and Clinical examination and laboratory testing were repeated after six months.

Method of Sampling:

It was calculated according the prevalence of women using levonorgestrel releasing intrauterine system and population size (5128), it was calculated through: $N = (t^2 \times p\ (1\text{-}p)) \div m^2$. Description: N =Required sample size t= Confidence level at 95% (standard value of 1.72) p= Estimated prevalence of disruptive behavior disorders. m = Margin of error at 5% (standard value of 0.05). Sample Size = N / (1 + (N/Population)). The sample size was estimated according to prevalence of present population size 5128 and prevalence of women using levonorgestrel. Assuming = 0.05, we calculated that we would need 50 women to achieve, a power of 80% (= 0.8).

Statistical Analysis

Results were tabulated and statistically analyzed using a personal computer using Microsoft Exel, 2016 and SPSS v. 21 (SPSS Inc., Chicago, IL, USA)**.** Statistical analysis was done using: Descriptive: e.g. percentage (%), mean and standard deviation. Analytical that includes Paired t test, and Mann-Whitney test. A value of P equal or less than 0.05 was considered statistically significant.

RESULTS

In the current study, mean age of the studied patients was 37.42 ± 9.11 years pretreatment increased to 38.15 ± 7.32 years after 6 months follow-up. There were no statistically significant differences between the studied patients regarding socio-demographic characteristics before and after 6 months follow up (Table 1). In addition, fasting blood glucose and cholesterol levels showed no statistically significant differences before and after 6 months follow up. Also, high-density lipoprotein level among the studied patients ranged from 53.1 to 66.7 with mean 62.04 ± 12.90 mg/dl pretreatment decreased 60.15 ± 9.11 mg/dl after 6 months follow-up. While, mean of low-density lipoprotein level was 91.05 ± 17.22 before treatment decreased to 88.72 ± 24.19 mg/dl after 6 months follow-up. High- and low-density lipoprotein levels showed no statistically significant differences before and after 6 months follow up of treatment (Table 2).

Table (1): Distribution of the studied patients regarding their socio-demographic characteristics before and after 6 months

	Pre-treatment	After 6 Month follow up	Paired t test	P value
Age/years: • Mean ± SD • Range	37.42 ± 9.11	38.15 ± 7.32	0.76	0.488
Height (m): • Mean ± SD • Range	1.65 ± 0.27 1.58 - 1.70	1.63 ± 0.58 1.58 - 1.70	0.94	0.270
Weight (kg): • Mean ± SD • Range	68.12 ± 1.80 57.5 - 72	72.40 ± 5.67 59.11 - 72	2.08	0.075
BMI (kg/m^2): • Mean ± SD • Range	21.16 ± 3.87 23 - 24.7	23.26 ± 2.08 23 - 24.9	2.13	0.061
WC (cm): • Mean ± SD • Range	81.01 ± 22.93 75 - 88	86.57 ± 11.54 75 - 91	1.07	0.067

BMI: body mass index WC: Waist circumference SD: Stander deviation

Table (2): Distribution of the studied patients regarding fasting blood glucose and cholesterol levels and high- and low-density lipid levels before and after 6 months

	Pre-treatment	After 6 Month follow up	Paired t test	P value
FBG (mg/dl): • Mean ± SD	82.25 ± 3.11	83.63 ± 7.88	1.55	0.082
Total cholesterol (mg/dl): • Mean ± SD	142.5 ± 16.72	138.67 ± 21.04	2.09	0.063
HDL - C > 60 (mg/dl): • Mean ± SD	62.04 ± 12.90	60.15 ± 9.11	0.78	0.352
LDL -C < 100 (mg/dl): • Mean ± SD	91.05 ± 17.22	88.72 ± 4.19	3.11	0.058

FBG: Fasting Blood glucose level SD: Stander deviation HDL: high density lipoprotein LDL: low-density lipoprotein

In the current study, mean of triglycerides level among the studied patients was 111.04 ± 35.89 pretreatment decreased to 109.33 ± 44.87 mg/dl after 6 months follow-up with no statistically significant differences before and after 6 months follow up of treatment (p = 0.415). While, VLDL-C level was not comparable before and after 6 months follow-up (p = 0.940). Mean systolic blood pressure among the studied patients was115 ± 5.33 (mmHg) pretreatment decreased to 110 ± 4.81 (mmHg) after 6 months follow-up. Also, systolic and diastolic blood pressure showed no statistically significant difference before and after 6 months follow up (p = 0.17, 0.985 respectively) (Table 3).

Table (3): Distribution of the studied patients regarding triglycerides, UDL-C levels, systolic and diastolic blood pressure before and after 6 months

	Pre-treatment	After 6 Month follow up	Paired t test	P value
TG < 150: • Mean ± SD	111.04 ± 5.89	109.33 ± 4.87	0.59	0.415
VLDL - C: • Mean ± SD	16.25 ± 3.45	16.11 ± 3.20	0.11	0.940
SBP (mmHg): • Mean ± SD	115 ± 5.33	110 ± 4.81	1.03	0.170
DBP (mmHg): • Mean ± SD	75 ± 2.14	70 ± 2.21	0.003	0.985

TG: Triglycerides level VLDL: very low-density lipoprotein SD: Stander deviation

In the current study, menstrual change was the most frequent among the studied patients (15 cases, 32.61%), followed by spotting in 6 cases (13.04%), then lower abdominal pain in 5 cases (10.87%). While, weight gain recorded the lowest frequent (2.17%). Regarding overall satisfaction with the method, most of the studied patients had very or somewhat satisfied (32 cases, 69.57%) and 14 cases (30.43%) had neutral or somewhat not satisfied, the same result for recommend the method (Table 4).

Table (4): Adverse effects and acceptability of the methods used

Adverse effects	Studied patients (No=46) 3 escape follow up expulsion 1	
	No.	%
▪ Spotting	6	13.04
▪ Menstrual change	15	32.61
▪ Lower abdominal pain	5	10.87
▪ Ovarian Cysts	3	6.52
▪ Headache	2	4.35
▪ Amenorrhea	3	6.52
▪ Acne – mood change	0	0.00
▪ Weight gain	1	2.17
Overall satisfaction with the method:		
▪ Very or somewhat satisfied	32	69.57
▪ Neutral or somewhat not satisfied	14	30.43
Would you recommend the method		
▪ Highly or somewhat agree	32	69.57
▪ Neutral or somewhat disagree	14	30.43

DISCUSSION

In present study, Socio- demographic characteristics of the studied women showed no statistically significant differences before and after 6 months follow-up. This is comparable to the mean age reported by **Gupta *et al.*** [8] in their respective study. This implies that an ideal age was above 30 years for the women who are opting for the use of LNG IUD. Also, **Kesim *et al.*** [9] found that baseline characteristics such as mean age, body mass index and exposure to tamoxifen therapy were similar in both groups. In the study done by **Singh *et al.*** [10], they found that in anthropometric data, significant reduction from baseline was seen in case of both BMI and waist circumference at 6 months. Other parameters did not show any significant change.

Similar data was observed by **Vasaraudze *et al.*** [11] where they found that the LNG-IUS has no significant adverse effects on any of these parameters, which could further lead to risk of any of the metabolic disorders. In contrast, **Bender *et al.*** [12] determined an increase in body weight and abdominal circumference.

On the other hand, **Kayikcioglu *et al.*** [13] assessed the possible effects of the levonorgestrel-releasing intrauterine system (LNG-IUS) on serum lipids and fasting blood glucose levels over a period of 1 year. Forty-eight women were enrolled in the study initially, but 33 (68.75%) women were eligible for control at the end of the first year, others were lost to follow-up. Seventeen women were treated with oral progestins and two were with oral contraceptives prior to the insertion of the LNG-IUS but either discontinuation due to systemic side effects or poor patient compliance, the treatments were changed to LNG-IUS three months later. There were no complications experienced during insertion.

In the current study, fasting blood glucose and cholesterol levels reported no statistically significant differences before and after 6 months follow-up. Metabolic studies concerning LNG-IUS are very limited. **Raudaskoski *et al.*** [14] found that combining LNG-IUS to transdermal estradiol reversed the improving in insulin sensitivity effect of transdermal estradiol. **Rogovskaya *et al.*** [15] concluded that LNG-IUS had no adverse effect on glucose metabolism and that its use in women with diabetes should be liberalized [16]**. Mascarenhas *et al.*** [17] found that it is strongly associated with an increased risk of CHD. In study by **Ng *et al.*** [18], they found no significant changes in the HDL/TC ratio and the mean HDL/ LDL ratio. In both groups, the mean HDL/TC ratio remained above 0.2, and the mean HDL/LDL ratio was above 0.3 at all sampling times.

The present study indicated that high- and low-density lipoprotein levels showed no statistically significant differences before and after 6 months follow up. Our results come in agreement with **Nilsson *et al.*** [19] who found a nonsignificant trend toward lower HDL-C concentrations in LNG-IUS users compared to nonusers. In a population-based cross-sectional Norwegian survey study, they found that the use of the LNG-IUS was associated with favorable non-HDL-C and TG concentrations and decreased HDL-C concentrations. They also found increasing levels of HDL-C with longer duration of use of the LNG-IUS [20]. Also, **Bender *et al.*** [12] concluded that each of the progestin methods could be regarded as being safe in their effects on lipid metabolism.

In the current study, systolic and diastolic blood pressures showed no statistically significant difference before and after 6 months follow up ($p = 0.17$ and 0.985 respectively)**.** The impact of LNG-IUS on blood pressure is another controversial issue. Since it does not contain estrogen, it is considered as safe for use by women with elevated blood pressure, but **Ronnerdag *et al.*** [21] reported a slight increase in blood pressure over 12 years of continuous use of LNG-IUS. Conversely, **Nilsson *et al.*** [19] found a slight decrease in both systolic and diastolic blood pressures after 1 year of use. **Raudaskoski *et al.*** [14] observed a decrease in systolic blood pressure at 3 and 6 months, whereas no change was observed in diastolic blood pressure. Our results are in discordance with **Nilsson *et al.*** [19] who found a significant decrease in diastolic blood pressure and a slight decrease in systolic blood pressure after 1 year of use and reported that it is a promising alternative for middle-aged hypertensive women. The mechanism of decrease is not known but requires further investigation. Research on middle-aged hypertensive women will shed light on this controversial issue [22].

In the current study menstrual change was the most frequent among the studied patients (15 cases, 32.61%), followed by spotting in 6 cases (13.04%), then lower abdominal pain in 5 cases (10.87%). While, weight gain recorded the lowest frequent (2.17%). In fact, nearly 25% of women discontinued using the LNG-IUS because of amenorrhea [(23)]. Approximately 20% of LNG-IUS users will be amenorrheic by the end of 12 months, and 70% of users will be oligomenorrheic or amenorrheic by 24 months [(24)]. In addition, though the systemic absorption is much smaller than with other progestin-containing contraceptives, there is some absorption and it can occasionally be associated with a variety of undesirable side effects such as ovarian cysts, acne, weight gain, depression and decreased libido. However, the device seems to be well tolerated overall [(25)]. Similar data were observed by **Hubacher *et al.*** [(26)] who found that about 25% of LNG IUS users reported common IUD side effects such as cramping/abdominal pain and backache. Also, in China, a randomized trial by **Wang *et al.*** [(27)] showed that irregular bleeding with the levonorgestrel subdermal implant was a dominant complaint and reason for removal, whereas amenorrhea was the dominant factor for the LNG IUS. In the analysis of menstrual diaries, incidence of prolonged bleeding and number of bleeding/spotting days was far higher in implant users compared to LNG IUS users.

In the current study, regarding overall satisfaction with the method, most of the studied patients had very or somewhat satisfied (32 cases, 69.57%) and 14 cases (30.43%) had neutral or somewhat not satisfied and the same result for recommend the method. A study by **Backman *et al.*** [(28)] that involved the evaluation of 17,914 questionnaires of current LNG-IUS users showed that 74% were very or fairly satisfied with it. User satisfaction correlated with the amount of information provided regarding different symptoms regardless of whether or not the patient actually experienced that specific symptom. In particular, the women who were warned of the possibility of amenorrhea were more satisfied than the women who were not. Similar data were observed by **Braniff *et al.*** [(29)] who found that patient satisfaction was high and similar in both groups. At six months postpartum, 90.5% of the study group were very satisfied or somewhat satisfied compared to 88.2% of the control group. Also, **Hubacher *et al.*** [(26)] found that nearly 87% of LNG IUS users were very satisfied with the method at 6 months compared to 75% of implant users. This gap was closed somewhat at 12 months as satisfaction levels of implant users rose. At 12 months, 78% of LNG IUS users felt that their bleeding pattern was highly acceptable compared to about 66% of implant users. A three-year study by **Baldaszti *et al.*** [(30)] found that the number of women who expressed that they were very satisfied with the LNG-IUS increased steadily with the duration of the treatment, with 29% after two weeks, 56% after two months, 69% after six months and 77% after 36 months.

CONCLUSION

Among the Egyptian, the LNG-IUS does not have any adverse effects on metabolic parameters, TGs, LDL and blood sugar levels. Most of the studied patients were very or somewhat satisfied with methods and 30.43% were neutral or somewhat not satisfied, the same result for recommend the method.

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