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Original Research Article

Impact of levonorgestrel intrauterine system on metabolic parameters

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ABSTRACT

Background: Hormonal contraceptive is suggested to affect parameters like body mass index, body weight, blood pressure (BP), blood sugar, lipid protein, and liver function test (LFT) but effect of LNG-IUS on those parameters is still uncertain. The aim of the present study was to study the effects of LNG-IUS on the metabolic parameters.
Methods: Sixty women who opted for LNG-IUS for various indications were included in the study. Lipid profile, liver function tests (LFT), glucose levels [fasting and post prandial (PP)], and hemoglobin (Hb) were tested. Bimanual genital examination and transvaginal-ultrasonography was done prior to LNG-IUS insertion. Any problems observed were recorded. The subjects were re-evaluated after 6 and 9 months on their subsequent visits. Data were analyzed using paired "t" test. P value of <0.05 was considered statistically significant.
Results: Mean age of the patients was 35.5±6.79 years. Maximum number 50 (83.3%) had abnormal uterine bleeding (ovulatory dysfunction, endometrial, iatrogenic, not yet classified) [AUB (OEIN)]. Mean pictorial blood loss assessment chart (PBAC) score of patients was 164.7±56.72 and mean Hb level 11.15±1.75g/dL. LNG-IUS showed no significant adverse effects on anthropometric parameters at 6- and 9-month follow-up. Significant change was seen in total cholesterol (TC), very low-density lipoprotein (VLDL) and high density lipoproteins (HDL) values at follow-up ($p<0.0001$).
Conclusions: In conclusion, amongst Asian population, the LNG-IUS does not have any adverse effects on metabolic parameters, TGs, LDL and blood sugar levels.

Keywords: Body mass index, Lipid profile, Levonorgestrel-releasing intrauterine system, Weight gain

INTRODUCTION

Levonorgestrel-releasing intrauterine system (LNG-IUS) is used in different modes of contraception. It was initially used to prevent pregnancy after an act of intercourse which was unprotected or inadequately protected by a contraceptive method. LNG at an oral dose of 1.5mg was registered as an emergency contraceptive based on the results of World Health Organization-sponsored clinical trials conducted primarily in the developing world. According to WHO, the LNG-IUS is now considered one of the most "efficacious, safe, and cost-effective medicines for priority conditions".[1] It is also used in treatment for menorrhagia, endometriosis, and endometrial hyperplasia; in combination with estrogen for hormone replacement therapy; as an alternative to hysterectomy; and to control heavy menstrual bleeding.[2] Since first becoming available 15 years ago, oral LNG has become available without prescription in most countries around the world given its well established safety profile and the importance of intake as soon as possible after unprotected intercourse. LNG-IUS is a T-shaped device composed of a cylinder containing 52mg of LNG. LNG thickens cervical mucus

and suppresses endometrial proliferation, thereby creating a hostile environment for sperm survival, thus preventing fertilization. LNG-IUS is safe and highly effective due to its direct progestogenic effect on the endometrium, making it an ideal method of contraception for many women. This device is easy to use, has few absolute contraindications, and results in few side-effects beyond changes in menstrual bleeding. After an LNG-IUS is inserted into the uterus, the menstrual bleeding pattern greatly changes in all users, as levonorgestrel is dispersed throughout the inner lining of the uterus. Due to decreased menstrual bleeding, many women find it desirable. But, the effect of LNG-IUS on metabolic parameters like body mass index (BMI), body weight, blood pressure (BP), blood sugar, lipid profile, and liver function test (LFT) is still unclear. There are few studies from India analyzing LNG-IUS effect on metabolic parameters.

This study is done in order to study the cardiometabolic characteristics of LNG-IUS users and its possible impact on the metabolic parameters (BP, BMI, blood sugar, and lipid profile).

METHODS

Inclusion criteria

- A prospective study was done for a period of 2 years whereby 60 cases of women opting for LNG-IUS for various indications (contraceptive/non-contraceptive uses) were included in the study.
- Each patient was provided with a written and verbal description of the research protocol and subsequently written and informed consent was taken from all the subjects for inclusion in this study.

Exclusion criteria

- Any patient with history of pregnancy, lactation, abortion in last 3 months, genital bleeding, uterine anomaly, uterine fibroid, acute pelvic inflammatory disease, carcinoma of breast, uterus and cervix, cardiorespiratory disorders, morbid obesity, and uncontrolled systemic hypertension were excluded from study.

A questionnaire was prepared, and every subject was enquired about age, duration of marriage, level of education, number of births, and status of menstruation, and the results were recorded on prescribed proforma. Subjects were questioned about demographic profile, i.e. age, duration of marriage, level of education, number of births, and status of menstruation and the results were recorded on prescribed proforma. General, systemic, and gynecological examinations of all subjects were performed. Bimanual genital examination and transvaginal-ultrasonography was done prior to LNG-IUS insertion and the status of bleeding, any side-effects, or any additional problems observed were recorded. Height, weight, BMI, waist circumference, hip circumference, waist hip ratio, mid-arm circumference, and BP [systolic (SBP) and diastolic (DBP)] were noted. Lipid profile, LFT, glucose levels [fasting and post prandial (PP)], and hemoglobin (Hb) were tested prior to the insertion, and at 6th and 9th month on their subsequent visits.

The LNG-IUS was inserted into the uterine cavity according to the standard insertion instructions in selected subjects and simultaneously the blood samples were taken. Following insertion, subjects were asked to follow-up at 6th and 9th month. The changes in menstrual blood loss was assessed by the pictorial blood analysis both pre LNG-IUS insertion and at follow-up visits. Expulsion or removal of the device was noted, and reasons were evaluated. Side-effects experienced by study, if any, were also recorded. Pictorial blood loss assessment chart (PBAC) score was calculated by asking about the menstrual history of the patients. Repeat blood glucose, Hb, lipid profile, and LFT were done in both follow-up visits, as well as the anthropometric measurements were taken.

Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 for Windows (paired "t" test). The used $p<0.05$ rule was applied to detect significant differences.

RESULTS

Total 60 patients were included in the study. The mean age of the subjects was 35.5±6.79 years with a range from 22-50 years (Table 1).

Table 1: Distribution of subjects based on their age group.

Age (years)	Frequency (n=60)	Percentage
21-30	16	26.7
31-40	32	53.3
41-50	12	20.0
Age year	35.5±6.79	22-50 (Range)

In present study all of our subjects were literate, and majority had middle level education. Majority was from upper lower class 21 (35.0%). Maximum number of subjects 50 (83.3%) were in the group abnormal uterine bleeding (ovulatory dysfunction, endometrial, iatrogenic, not yet classified) [AUB (OEIN)] patients, followed by AUB (leiomyoma) [AUB (L)] 23 (38.3%), AUB (adenomyosis) [AUB (A)] 20 (33.3%), and those for contraception 18 (30.0%). The mean menstrual cycle pattern or PBAC score of patients was 164.7±56.72 with a range 76.2-386. Initially, mean Hb was 11.15±1.75g/dL, at 6 months 11.82±1.16g/dL, and 12.82±1,06g/dL at 9 months (Table 2). In respect of both these parameters, the variation or the change in the values before insertion and after 6 or 9 months was significant

(P< 0.05). Anthropometric data of day 1 was compared to 6- and 9-month follow-up and was found significant. BMI and waist circumference at 6 months showed significant reduction but reverted to previous levels at 9 months. The other anthropometric parameters did not show any significant change (P <0.05).

Table 2: Mean value of baseline and at follow-ups of PBAC score and hemoglobin level (g/dL) in study subjects.

	At enrolment Mean±SD	After 6 months Mean±SD	After 9 months Mean±SD
PBAC score	164.7±56.7	122.3±38.5**	94.3±35.34**
Hemoglobin	11.15±1.75	11.82±1.16*	12.82±1.06**

*P <0.05; **P <0.0001 between enrolment and 6 or 9 months.

Table 3: Mean value of baseline and at follow-ups of BP (mmHg) in study patients.

Blood pressure (mmHg)	At enrolment Mean±SD	After 6 months Mean±SD	After 9 months Mean±SD
Systolic	120.38±5.62	120.83±4.71	122.18±4.59
Diastolic	74.57±4.59	78.76±4.77	74.78±4.84

P=Non-significant (p>0.05).

Table 4: Mean blood glucose values at enrolment and at follow-up in study subjects.

Blood glucose (mg/dL)	At enrolment Mean±SD	After 6 months Mean±SD	After 9 months Mean±SD
Fasting	86.37±6.61	88.25±5.92	87.28±6.32
Post prandial	127.35±8.33	128.88±8.18	127.55±6.94

P=Non-significant (p>0.05).

Table 5: Mean lipid profile at time of enrolment and at follow-ups of studied subjects.

Lipid profile (mg/dL)	At enrolment Mean±SD	After 6 months Mean±SD	After 9 months Mean±SD
Total Cholesterol	183.77 ±26.23	199.36±27.39*	188.43±19.48
Triglycerides	123.75 ±12.29	119.95±12.42	122.58±10.73
LDL	103.03±15.27	107.37±17.90	104.55±16.19
HDL	48.02 ±3.69	54.35±4.50**	60.31±5.21**
VLDL	25.2 ±3.19	39.25±4.03*	42.05±5.11*

*P <0.05; **P <0.0001 between enrolment and 6 or 9 months; non-significant (p>0.05).

Initially, 48.33% women were having weight in normal range where as 45.0% women were overweight. At 6 months, 53.3% subjects were in the normal range while 48.3% subjects were in normal range at 9 months. Not much difference exists in respect to BMI from the time of enrolment to 9 months. On the basis of waist hip ratio, maximum subjects 45.0% were on low risk (waist hip ratio 0.80 or below). On follow-up, 50% subjects were in the low-risk range and at 9 months, 56.7% subjects were in low-risk range. At enrolment, mean SBP was 120.38±5.62 (mmHg) range 109-131, and the mean DBP was 74.57±4.59 (mmHg) range 68-83. The difference between the values, at the time of enrolment and after 6 or 9 months was not significant (P>0.05) (Table 3).

Fasting blood glucose was <100 mg/dL in all 60 subjects and 56 (93.33%) had normal PP level. At enrolment, mean fasting blood glucose was 86.37±6.61 (range 70-98mg/dL), and mean PP blood glucose was 127.35±8.33 (range 108-145mg/dL). The difference of fasting and PP blood sugar level was not significant from time of enrolment and at 6 months and 9 months with p value >0.05. Thus, indicating no increase in risk of diabetes mellitus in patients using LNG-IUS (Table 4).

Initially, 41 (68.33%) subjects had total cholesterol in normal range while 19 (31.67%) were in borderline range. At 6 months, the number of subjects in the borderline had increased to 46 (76.67%). At 9 months, 46 (76.67%) were in normal range group while 14 (23.33%) remained in borderline group. None of the patients had total cholesterol in high range.

Table 5 shows the mean values of total cholesterol, triglycerides, LDL, high-density lipoprotein (HDL), very low-density lipoprotein (VLDL) at enrolment, 6 months, and 9 months follow-up. Significant change was seen in total cholesterol from enrolment to 6 months. Similarly, the increase in HDL values was found to be highly significant at 6- and 9-months follow-up (p<0.0001). Despite increase in the mean, the values were in the same range group.

DISCUSSION

LNG-IUS is highly efficacious, providing effective contraception for up to five years. Due to safety, efficacy, and less side-effects, LNG-IUS is used worldwide. The product releases small amounts of progestin into the uterus and improves contraceptive action compared with earlier inert plastic devices. LNG-IUS has highest effectiveness levels compared to other similar contraceptive (combining the highest product continuation rates with over 99% efficacy). Few studies have been done to study the impact of LNG-IUS on metabolic parameters. In present study, mean age of the subjects was 35.5±6.79 years. This is comparable to the mean age reported by Arlıer S et al and Gupta T et al in their respective study.[3,4] This implies that an ideal age was above 30 years for the women who are opting for the use of LNG IUD. In the present study, the maximum subjects 40 (66.7%) had middle level education. Arlıer S et al, Geetha P et al and Gupta T et al, in their studies reported that the patients belonged to lower socioeconomic strata and were less educated.[3-5] In the present study, the indication of LNG-IUS insertion observed in majority of subjects was AUB (OEIN). Singh K et al, observed that 69% patients had dysfunctional uterine bleeding as the common indication of LNG-IUS insertion.[6] In this study, Hb increased in subjects at 6th and 9th months and PBAC score reduced at 6th and 9th months, indicating reduction in menstrual blood loss and improved quality of life. Bitzer J et al, noted 96% reduction in PBAC score.[7] Jayanthi P et al reported PBAC score as 206±104 and median Hb concentrations 11.2-13.2g/dL.[8] In the present study, SBP was 120.38±5.62mmHg, DBP 74.57±4.59mmHg, and mean fasting blood glucose 86.37±6.61mg/dL. Vasaraudze I et al, reported SBP as 121.92 (15.88), DBP 81.53 (14.19) while fasting glucose 88.38mg/dL, comparable to present study.[9] The occurrence of high BP during use of an LNG-IUS has been studied several times, but none of the studies, with a follow-up of 1–10 years could find a relation.[2] Total cholesterol increased at 6 months; HDL and VLDL increased at 6 and 9 months. Although there was increase from baseline, all were within the same range. Thus, it can be considered a safe alternate therapy that can be given to older females without posing any high risk for CVD or any metabolic disorder. A longer follow-up with large number of subjects will only lead to know the effect of LNG-IUS on lipid profile. Similar data was observed by Vasaraudze I et al.[9] In a randomized comparative study among Asian population, LNG-IUS does not have any adverse effects on lipid metabolism.[10] In present study, 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 I et al.[9] This shows 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 NM et al determined an increase in body weight and abdominal circumference.[11] In the present study, the LFT was analyzed and the change in almost all the parameters of LFT were found to be statistically insignificant ($p>0.05$). Very limited studies have been performed on effect of LNG-IUS on the metabolic parameters. At present, it is not clear yet whether the identified changes would continue to progress during the long-term use of the LNG-IUS.

The purpose of the study was to clarify the cardiometabolic characteristics of LNG-IUS users and the possible impact of the LNG-IUS on metabolic parameters. Present study shows that the LNG-IUS does not have any adverse effects on BMI, Total Cholesterol, Triglycerides, LDL, LFT, blood pressure, blood sugar but long-term study involving large number of subjects will reveal more clearly the long-term metabolic effects of LNG-IUS. There are few studies which focus on LNG-IUS and there is a huge gap between our knowledge and what the time demands. The current research regarding LNG-IUS in Indian population will highlight its effect on metabolic parameters.

CONCLUSION

To conclude, LNG-IUS is an effective and acceptable form of contraception. But hormonal contraceptives are associated with serious metabolic side-effects; therefore, study of effect of LNG-IUS on metabolic parameter is must. LNG-IUS in this study is found to have no significant effect on various metabolic and anthropometric parameters but long-term effects on metabolism still needs to be studied.

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