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Evaluation of non-contraceptive benefits of LNG-IUS: A clinical study

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Abstract
Introduction: IUCDs are the most widely used and effective contraceptive methods and are safe. Huge variety of IUCDs are available which include inert, copper containing, and medicated with levonorgestrel or indomethacin. LNG has been explored for its non-contraceptive benefits by various researchers and found to be effective for women and adolescents as first line therapy with heavy menstrual bleeding and is associated with improved dysmenorrhoea.so we did a two year perspective study in deptt of obs and gynae at GMC Patiala to assess the role of LNG-IUS IN various gynaecological indication otherthan contraception.
Material and Methods: Women with heavy menstrual period, dysmenorrhea or both who reported in the OPD were examined, including breast and pelvic examination. USG was done to note various pathologies like fibroid, endometriosis, endometrial hyperplasia, adenomyosis and functional ovarian cyst. This was followed by endometrial biopsy. After the biopsy report was available, decision for LNG-IUS insertion was taken. LNG-IUS was inserted, under all sterile conditions without anaesthesia. After insertion, patient was followed up at 1-, 3-, 6- and 12-month interval for menstrual pattern change any complications compliance on part of patient.
Results: A total of 30 patients were enrolled over a period of two years. 28 patients were in the age group 30-50 years and only 2 patients were post-menopausal. 56.6% had rural background, 43% were illiterate and 83.3% were multipara. In 50% of the women, the chief complaint was heavy menstrual bleeding with dysmenorrhea and 36% had heavy menstrual bleeding alone. 6.6% had dysmenorrhea alone and another 10% reported with irregular bleeding. According to PALM-COIEN classification, AUB-A was diagnosed in 16.6%, AUB-L in 30%, AUB-O in 40%, AUB-M in 3.3%, endometriosis in 13.3%. LNG-IUS was not used as contraception or HRT in any of the cases.
On post insertion follow up after one month, 90 percent had relief from heavy menstrual bleeding. At six-month follow-up, 23.3% reported spotting and 60% reported normal flow during periods. After one year 73.9% patient had normal flow and 13% patients achieved amenorrhoea.
The irregular bleeding or spotting was managed by giving supportive therapy in form of reassurance in 30%, NSAIDS in 16.6%, and norethisterone in 46.6%. Ormeloxifene and OCPs were given in 3.3% each and response was satisfactory.
At one year follow up it was seen that 76.6% patients continued with LNG IUS and found it comfortable with enhanced quality of life.
Conclusion: LNG-IUS is a better choice for the management of endometrial hyperplasia simple or complex, with or without atypia, AUB, adenomyosis and endometriosis. LNG-IUS can be a good alternative to hysterectomy.

Keywords: levonorgestrel intrauterine system, menstrual bleeding, endometriosis, endometrial hyperplasia

Introduction
IUCDs are the most widely used and effective contraceptive methods and are safe. Huge variety of IUCDs are available which include inert, copper containing, and medicated with levonorgestrel or indomethacin.
The LNG -IUS (levonorgestrel releasing intrauterine system) was introduced by Schering -ox, Finland which released *in vitro* 20 micrograms of levonorgestrel per day. LNG-IUS contains 52 mg of levonorgestrel which is dispensed in polydimethylsiloxane frame which stays inside the uterus and very small amount is released in blood. Mechanism of action of LNG IUS is similar to LNG implant /minipills but with lower peak of serum levels 0.1 to 0.4 ng/ml. 20 µg of LNG-IUS is released every 24hrs and it decreased to 11 µg /24hrs by end of 5 yrs. LNG thickens cervical mucus and suppresses endometrial proliferation creating hostile environment for sperm survival by inhibiting motility and capacitation to prevent fertilisation.

It produces endometrial thinning cum fragile superficial vessels preventing implantation [2].

LNG has been explored for its non-contraceptive benefits by various researchers and found to be effective for women and adolescents as first line therapy with heavy menstrual bleeding and is associated with improved dysmenorrhoea [1]. It was found to be satisfactory, effective and economical alternative to medical surgical treatment of menorrhagia [2, 4, 5]. Associated medical diseases in which LNG IUS can be used for treatment of HMB are obesity, severe anaemia, coagulopathies where surgery is either contraindicated, is high risk or is not affordable because of high cost [5, 6, 7, 8].

LNG has been associated with irregular spotting for up to 6weeks after insertion and is associated with progressive amenorrhoea [11-15]. Irregular bleeding if associated is treated by various methods like cyclical progesterone or with raloxifene or simple reassurance [9, 13]. Other side effects noticed with LNG are anxious depressive disorders, sexual disorders, increased weight gain and pain [11, 12]. So, a study was conceptualised to evaluate various non contraceptive uses and its side effects like irregular spotting through first year of its use and its management by different agents.

Aims and Objectives

- To evaluate LNG-IUS as a therapeutic alternative to hysterectomy in AUB, Endometriosis, Fibroid uterus.
- To study side effects and their management.
- To find its continuation v/s discontinuation rates.

Material and Methods

The present study was undertaken in Department of Obstetrics and Gynaecology, GMC, Patiala for a period of two years from 2017 to 2019 as a prospective interventional study. Consent for participation in the study was taken. Women with heavy menstrual period, dysmenorrhea or both who reported in the OPD were examined, including breast and pelvic examination. USG was done to note various pathologies like fibroid, endometriosis, endometrial hyperplasia, adenomyosis and functional ovarian cyst. This was followed by endometrial biopsy. After the biopsy report was available, decision for LNG-IUS insertion was taken. LNG-IUS was inserted, under all sterile conditions without anaesthesia.

After insertion, patient was followed up at 1-, 3-, 6- and 12-month interval. The menstrual pattern was noted and USG repeated to compare the changes with initial USG findings. For the abnormal bleeding pattern following LNG-IUS, oral progesterone v/s SERMs were compared. Exclusion criteria included pregnancy, DVT, STDs, liver disease, recent trophoblastic disease, bacterial endocarditis, uterine pathologies obliterating uterine cavities.

Results

A total of 30 patients were enrolled over the period of two year, who presented in Gynae OPD with chief complaint of heavy menstrual period with/without dysmenorrhea. 28 patients were in the age group 30-50 years and only 2 patients were post-menopausal. 56.6% had rural background, 43% were illiterate and 83.3% were multipara. (Table No 1).

Table 1: Demographic characteristics

Age (in years)	No. of patients	Percentage
30 TO 40	10	33.3
41 TO 50	18	60
51 TO 60	2	6.6
Education Status		
Illeterate	13	43
matric	6	20
graduate and above	11	36
Rural/Urban		
Rural	17	56.6
Urban	13	43.3
Parity		
Primipara	5	16.6
Multipara	25	83.3

In 50% of the women, the chief complaint was heavy menstrual bleeding with dysmenorrhea and 36% had heavy menstrual bleeding alone. 6.6% had dysmenorrhea alone and another 10% reported with irregular bleeding. 16.6% of women were obese with BMI >30 and 25% had diabetes, hypertension or both with distribution as shown in the table. 6.6% of women had heart disease and gall stones each. 3.3% had IITP, spine surgery, history of myomectomy, hypothyroidism, bronchial asthma and breast surgery. (Table No 2)

Table 2: Medical/Surgical Comorbidities in patients

Medical condition	No of patients	%age
BMI>30	5	16.6
Diabetes	3	10
Hypertension	4	13.3
Diabetes and hypertension	2	6.6
Gallstones	2	6.6
ITP	1	3.3
Bronchial asthma	1	3.3
Heart disease	2	6.6
Spine surgery	1	3.3
Diagnostic laparopscoy for endometriosis	1	3.3
Breast surgery	2	6.6

76% reported with moderate anaemia and 6.6% with severe anaemia. USG findings revealed adenomyosis in 16.6%, functional ovarian cyst in 13.3% with most commonly associated finding of fibroids in 30% of the patients. Endometrial thickness was more than 8mm in 66.6% of pts. The utero-cervical length was >7 cm in 16.6% and 8cm in 30%, 9cm in another 30% and >10 cm in 13.3%. Uterine cavity was regular in 93.3% of patients. Histopathological findings are as shown in the Table No 3.

Table 3: Endometrial Histopathlogy

Histopathology	No of patients	% age
Proliferative phase	10	33.3
Secretary phase	9	30
Disordered proliferative phase	4	13.3
Simple endometrial hyperplasia without atypia	5	16.6
Complex endometrial hyperplasia without atypia	1	3.3
Adenocarcinoma well differentiated with squamoid differentiation	1	3.3

According to PALM-COIEN classification, AUB-A was diagnosed in 16.6%, AUB-L in 30%, AUB-O in 40%, AUB-M in 3.3%, endometriosis in 13.3%. (Table no.4) LNG-IUS was not used as contraception or HRT in any of the cases.

Table 4: Final diagnosis

Indication for insertion	No of patients	%age
AUB -A	5	16.6
AUB -L	9	30
AUB-M	1	3.3
AUB -O	12	40
Endometrosis	4	13.3

On post insertion follow up after one month, 90 percent had relief from heavy menstrual bleeding (60% reported spotting, 23.3% reported moderate flow but not heavy flow,3.3% each reported amenorrhoea and normal flow). Rest 10% still had heavy flow. At six-month follow-up, 23.3% reported spotting and 60% reported normal flow during periods. After one year 73.9% patient had normal flow and 13% patients achieved amenorrhoea. The irregular bleeding or spotting was managed by giving supportive therapy in form of reassurance in 30%, NSAIDS in 16.6%, and norethisterone in 46.6%. Ormeloxifene and OCPs were given in 3.3% each and response was satisfactory. Repeat biopsy after 6 months was done in a patient of endometroid carcinoma with squamous differentiation stage 1a which came out to be same with improvement in symptoms. Later patient was lost to follow up. Dysmenorrhoea was reported by 17 patients and 12 got a relief from dysmenorrhoea.

At one year follow up it was seen that 76.6% patients continued with LNG IUS and found it comfortable with enhanced quality of life as 6.6% opted for hysterectomy as they continued to have heavy bleeding and pain. One of these patients was having fibroid uterus as well. Another 6.6% of patients got it removed as they were not satisfied with its use and switched to alternative medicine. In three patients it got expelled spontaneously which was noticed on repeat USG.

Discussion

Perimenopausal age group of women is surrounded by plethora of menstrual problems for which earlier hysterectomy was the only answer but as the physiology and pathology became clearer with advancing research there came many options to treat these problems. Most of the women in developing and developed countries, who suffer from AUB opt for hysterectomy because of the loss of working hours, money, costly healthcare and associated morbidity with AUB. Various medical and surgical methods available for heavy menstrual bleeding are like Prostaglandin synthetase inhibitors, anti-fibrinolytic agents, OCPs and endometrial ablation (Trans cervical resection of endometrium or thermal balloon ablation), have just 20-50% efficacy [2]. LNG appears to be a boon for women with heavy menstrual bleeding provided they are adequately counselled [4]. In our study, 90% of the patients got relieved of heavy menstrual flow within one month of its use and similar trends were noticed by other authors [2, 4, 5, 7, 12, 15]. (Table No 5).

Table 5: Comparison of Results with various studies

Author & Study	Decrease in Blood Loss	Decrease in Dysmenorrhea	Continuation rate	Hysterectomy
Beatty and Blumenthal 2009	86-97%	-	90%	-
Gallos *et al*. 2013	84%	-	-	-
Uma Pandey 2016	80%	-	80%	20%
GARG And SONI A 2016	93%	76%	90%	6%
Benipal *et al*. 2018	85%	-	98%	1.92
Beckert V *et al*. 2019	54%	-	-	-
Chen Ba *et al*. 2019	74.7%	-	-	-
Margatho D *et al*. 2020	-	Vas score decreased	-	-
Present Study	90%	70%	76.6%	6.6%

LNG-IUS when compared with oral progesterone's is a better first line management in endometrial hyperplasia because of 94% regression rate as compared to 84% [3, 7]. Mandel Baum *et al*., RS *et al*. compared the effects of LNG-IUS with systemic progesterone in complex atypical endometrial hyperplasia in 245 women and found (78.7% vs 46.7%) higher rate of complete response and lower progression rate to cancer in LNG-IUS group (4.5% vs 15.7%) [9].

Endometriosis is a significant problem affecting 5.7% of women of reproductive age group causing chronic pelvic pain, dyspareunia, infertility and dysmenorrhea, affecting the quality of their life. The hypoestrogenic effects of medical treatment like Depot Medroxyprogesterone acetate, Danazol, gonadotrophin realising hormone analogues affected the compliance of the patients and higher discontinuation rate. This led to the use of LNG-IUS as an alternative. In our study, 17 patients who came with dysmenorrhea and heavy menstrual bleeding and diagnosed on USG as adenomyosis and endometriosis, 12 patients were relieved of dysmenorrhea within 6 months of LNG-IUS insertion cosistentent with findings of other authors. In adenomyosis, LNG-IUS causes decidualization and atrophy of endometrium. Decreased blood flow and downregulation of oestrogen receptors in glandular and stromal endometrial tissue leads to atrophy and shrinkage of adenomyosis foci in the myometrium. This allows myometrium to contract better and decreases blood loss and the size of the uterus [2, 5, 7, 17].

Endometrial hyperplasia may be simple or complex, with or without atypia, is another indication where LNG-IUS is being used with 100% response rate.

Fertility preservation is the main requirement in endometrial cancers, LNG-IUS has been tried and lesion have regressed in 70-75% cases of Stage 1A endometrioid endometrial cancer and atypical hyperplasia [18]. In our study, we had just one case of endometrial cancer who was not medically fit for hysterectomy, so LNG-IUS was given with dramatic decrease in blood loss and improvement in general condition through 6 months post LNG-IUS. Histopathological findings were same on repeat biopsy and there after that patient was lost to follow-up.

In our study, 30% of patients had fibroid who reported with heavy menstrual bleeding and dysmenorrhea and found to have endometrial hyperplasia which might be associated with hyper estrogenic state. Uterine cavity was not distorted by fibroids and fibroid size did not exceed 3cm. LNG-IUS was given and only one patient expelled it, another one patient discontinued it following persistent heavy menstrual bleeding and another got it

removed and underwent hysterectomy. Uma Pandey too reported 20% hysterectomy rate in her study. (Table no.5)

LNG-IUS is usually well tolerated but its most common side effects are menstrual bleeding cycle change and spotting off and on, maybe breakthrough bleeding. Most authors report decrease in number of bleeding days and improvement in symptoms from 1st through 3 months of insertion [12, 13, 14, 15, 16]. The treatment of this breakthrough bleeding by oral progesterone or by SERMs were not much different [13]. In our study we found SERMs giving better control than oral progesterone.

Overall use of LNG-IUS was associated with good results with increase in quality of life but it needed lots of persuation to go for this method as it resembled CuT. Various myths attached with CuT affected the choice of LNG-IUS over hysterectomy. Second was the cost factor which was a major hurdle in acceptance of the method. Third was the refusal for follow up visits and repeat biopsy requirements as most pts want once and for all treatment. Larger studies are required to further authenticate its use for non contraceptive uses.

Conclusion

It is being concluded that LNG-IUS is a better choice for the management of endometrial hyperplasia simple or complex, with or without atypia, AUB, adenomyosis and endometriosis. LNG-IUS can be a good alternative to hysterectomy, and is akin to medical hysterectomy in present times, which is cost effective, time saving, does not require anaesthesia and decreases morbidity.

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