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Dr. Athmar Ali Mousa Fridawi
MBCHB DOG, Dep. of obstetrics and gynecology (family planning), Al- Imamain Al-Khadimain Medical City, Baghdad, Iraq

Dr. Rafida Nasif Jasim
M. B. Ch. B, DOG, Department of Obstetrics and Gynecology, Abu Ghraib general Hospital, Iraq

Dr. Maha Ismaeel Khudhuer
M. B. Ch. B, DOG, Department of Obstetrics and Gynecology, Al-Karama general Hospital, Iraq

Corresponding Author:
Dr. Athmar Ali Mousa Fridawi
MBCHB DOG, Dep. of obstetrics and gynecology (family planning), Al-Immamain Al-Khadimain Medical City, Baghdad, Iraq

Dramatic response of Mirena (levonorgestrel intrauterine system) in treatment of menorrhagia

Dr. Athmar Ali Mousa Fridawi, Dr. Rafida Nasif Jasim and Dr. Maha Ismaeel Khudhuer

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Abstract
Background: Menorrhagia is a type of menstrual disorder that is characterized by the presence of red vaginal discharge from the uterine cavity on a regular basis, but excessive in quantity (greater than 80 ml) and / or duration (greater than 7 days).
Objective: To study the dramatic response of levonorgestrel intrauterine system (LNG-IUS) Mirena for treatment of menorrhagia during its use as contraceptive.
Matera and methods: 30 women between 30 and 50 year with menorrhagia were included in a study over two year. Response was assessed monthly for first 4 month and then yearly for maximum 2 year.
Result; Mirena caused decrease in blood loss (MBL) in 16.7% of the patients at 4 month, 73.3% decrease in(MBL) by one year and 100% decrease by 2 years, and improved the mean Hb level in 100% of the patients after 2 years. Mirena has an effective in treatment of abnormal uterine bleeding and this made surgical intervention (Hysterectomy) is last choice.
Conclusion:
LNG locally released on endometrium cavity is both a safe and reliable method of abnormal uterine bleeding treatment.

Keywords: Menorrhagia, Mirena, LNG, IUS

Introduction

Definition and importance of the menorrhagia

Menorrhagia is a type of menstrual disorder that is characterized by the presence of red vaginal discharge from the uterine cavity on a regular basis, but excessive in quantity (greater than 80 ml) and / or duration (greater than 7 days) [1-3]. Deep down, menorrhagia translates an excessive menstrual loss [4], which produces social, labor or sexual disorders in a woman's life, as well as medical risks as a result of iron deficiency anemia [5]. Excessive uterine bleeding is the main annoyance of women who attend the gynecologist and account for two thirds of hysterectomies and most endometrial ablations [6, 7].

Family planning has been an important part of social development for thousands years. Egyptians first use contraception spermicides and barrier methods [8]. However, it was not until the second half of the twentieth century that reliable contraceptive method became commonly available. Progesterone containing contraceptive becoming more and more popular and come in different forms, including combined oral contraceptive pill subdermal, Implanon, progestin only pill, emergency contraception, medicated intrauterine contraceptive device. This study concentrate on Progesterone-releasing IUS. The first natural progesterone-releasing system IUS (Progestasert) contained 38 ug of progesterone, released rate of 65 ug daily for one year, 6 and have failure rate of 2% [1].

In 1990 a new Mirena was introduce replacing the old. Its major advantage included dose of LNG 14-20 a five year life cycle and decrease in menstrual blood loss [9].

Now there are two types of commercially available, Mirena Bayer, Leverkusen, Germany, contain 3mg LNG which released into Utrine cavity at a constant dose device of 20 ug per day for five year [10].

A new lower dose the LNG-14 IUS (Skyla; Bayer) contain 13.5 mg LNG which released at rate of 14 ug day for 3 year [11].

Pharmacology

Progestins; the term was coined to described synthetic progestational steroids and to differentiate them from natural progesterone. Progestins synthesized by minor structural changes to progesterone, testosterone, and more recently spironolactone [12], which lead to marked changes in biological activity of the newly synthesized steroid [13].

LNG (D {-} 1-1 7B-hydroxy-17 a-ethinyl-13B ethyl-14-gonen-3-one), a synthetic second-generation progestin chemically derived from 19-nortestosterne [14], is six times more potent than progesterone, but also has strong androgenic properties and binding globulin [15].

LNG can be administered using a multitude of delivery mechanism. Oral LNG rapidly absorbed, circulating hormone unbounded [16]. It metabolized by hydroxylation at carbons 2 and 16 to produced metabolites that circulate predominantly as sulfates in blood and then excreted as glucuronides in urine. Locally released LNG, is absorbed into the systemic circulation, reaching a plateau of 100-200pg/ml, a few weeks after intrauterine insertion [17]. This plasma level is lower than what is seen with LNG implant, combined oral contraceptive pill, and the minipill, and is not enough to suppress ovulation.2 Compared to atypical oral daily dose of 150 ug, the plasma level with LNG delivered through the LNG -20 IUS is only 4% -13% of levels observed after oral LNG [17].

Efficacy, effectiveness and cost-effectiveness

LNG 20IUS have been shown to be an effective, reliable, and reversible method of contraceptive. The LNG IUSs has come from studies on LNC-20 IUS, as the LNG-14 system is relatively new. Randomized study compared with other types of intrauterine device and combined oral contraceptive pill show cumulative failure rate for the LNG IUS was better than with traditional copper-releasing intra uterine devices (1.1 vs 1.4 per 100 women) [18, 19].

Cost effectiveness is another important factor in choice of suitable contraception, especially in areas with limited health budgets0.After 5 year of the use; the comparative effectiveness of the LNG IUS was the highest (98.9%) of all reversible contraceptive method. The cost –effectiveness analysis also showed the superiority of the LNG IUS over all other reviewed methods [20].

Depending on the method of administration, LNG has several contraception properties; the mechanism of oral LNG is suppression the secretion of hypothalamic gonadotropin-releasing hormone that preventing the mid-cycle luteinizing hormone surge and suppressing ovulation [21].

The major mechanism of action of LNG IUS is by suppression effect on the endometrium, including glandular atrophy and decidualization of the stroma [22].

LNG also causes down regulation of the local endometrial estrogen receptors, rendering them less responsive to circulating estradiol 21 and leading to thinning of endometrium.

Also help the expression of a protein that prevents binding of sperm to zona pellucida, inhibiting fertilization, and is usually absent in the fertile days of the mid-cycle until the fifth postovulatory day. The other mechanism of LNG is by making the cervical mucus thicker rending it hostile to sperm [22]. This combined with its endometrial effect; inhibit sperm motility function inside the cervix uterine body, and fallopian tubes.

Patient counseling; prior to insertion is vital for improving compliance and reducing anxiety accompanied with unexpected changes in women menstrual pattern. Furthermore explanation to women are required; the type of analgesia, side effect the cost, failure rate , patient consent is necessary [23].

Fig 1: Mirena system

Time of insertion

IUSs can inserted within 7 days of the onset of menstruation or at any time during the menstrual cycle, but care should be taken to be sure that the women is not in her early weeks of pregnancy. In cases of amenorrhea or in women who were not compliant with previous forms of contraception, a pregnancy test should be obtained at least 2 weeks after her test of unprotected intercourse. Backup method of contraception should be used for first 7 days after IUS insertion [24].

For postpartum women immediate insertion not recommended after complete abortion and in the absence of sepsis or bleeding, insertion can be perfumed immediately [25].

Analgesia

LNG IUS insertion is pain free, multiparas women required cervical dilatation or with history of previous painful intrauterine device insertion may be benefit from pre-insertion analgesia. Trial on use of topical cervical analgesia (lidocaine) [19, 20]. Nerve block (Para cervical block) using 10-20 ml of 1% lidocaine injection to a depth of 1cm should also be considered when analgesia is required.

Proper insertion procedure

The fundal position in uterine cavity provides excellent protection against pregnancy, low rate of removal for bleeding, and total suppression of endometrial growth.

Prevention of infection, screening for sexually transmitted disease and excluding cervicitis or vaginitis are important steps before insertion. the risk of pelvic inflammatory is reported to low (0.5%) in a new user [23].

In case of PID detected after insertion intrauterine device not need to be removed per se, but treatment should be started and prevent re infection If infection not resolving with treatment, then temporary removal of device should be consider. In general, antibiotics prophylaxis provides [23], and is not recommended [22], Additionally, the American Heart Association does not recommended endocarditis prophylactic for intrauterine device insertion in the absence

of pelvic infection [22, 23].
LUG IUS removed after five year. The LNG IUS recently used as a first line in treatment of heavy menstrual cycle or menorrhagia, and acts alternative to surgery (hysterectomy). An estimated 9.8 million women worldwide use the LNG –IUS, this usage mainly as contraceptive, but the added health benefit of reduced menstrual bleeding and less anemia make this an attractive option to many women worldwide. This system reduced menstrual loss up to 96% after one year. Local action of progestogen –related side effect are much less than with oral agents. The LUG IUS made revolution in treatment of anemia by accounted for much of the total 5-year cumulative discontinuation rate for bleeding problem [21].

Short-term side effect

1. Mild lower abdominal and back pain, (occur in half of women).
2. W0men may notice side effect related to the androgenic activity of LNG (nausea, headache, breast tenderness) [15, 24].
3. Menstrual disturbances are also common during the first 3 month of use [24].

Long-term side effect

1. Bleeding frequency decreased, leading to hypo amenorrhea [19, 26] (due to endometrial thinning and atrophy due to prolong effect on endometrium)
2. Unlikly LNG IUSs have not been linked to hypertension. weight gain, hyper glycaemia, hyperlipidemia hypercholesteremic reduced bone mineral density, increased metabolic cardiovascular and inflammatory, there's no evidence of increased risk of venous thromboembolism, stoke or myocardial infarction [27].
3. Functional ovarian cyst are commonly seen in women using the LNG IUS, with increased incidence that varies between 5%and 30%, which resolve spontaneously within first new month.
4. Risk of ectopic pregnancy (due to progesterone effect on peristalsis movement) Randomize study 0.2-0.4 per 1,000 women per year [16], which is lower that seen with other commonly used intrauterine devices.

Side effect common to intrauterine devices

1. Pelvic inflammatory disease
2. Utrine perforation (rarely). Side effect associated with the new lower –dose intra uterine system: When compered simultaneously, as the dose of LNG increased, the total days of bleeding and spotting decreased.
3. Change in menstrual patterns; amenorrhea, hypo menorrhea and break through bleeding. Amenorrhea while be mistaken for pregnancy or menopause pregnancy test must be done to exclude ectopic pregnancy

Acceptability, user satisfaction, and quality of life
The efficacy of contraceptive measured by pregnancy or failure rate, the LNG IUS well accepted by women [21].

Aim of the study: To study the dramatic response of levonorgestrel intrauterine system (LNG-IUS) Mirena for treatment of menorrhagia during its use as contraceptive.

In nulliparous women, the LNG IUS and combined oral contraceptive pills had similar continuation. Also associated with less dysmenorrhea and inter- menstrual bleeding and spotting and significantly fewer bleeding days [8].

Materials and methods
A thirty women their aged between 35-46 years old with menorrhagia, where included in prospective study which was performed in family planning, part from gynecology department of AL Khadymia Teaching Hospital in Baghdad from 15 of August 2014 to 20 of September 2016.

Data collection
Pregnant women completed pre-coded questionnaires after formal consent. The questionnaires included personal information (age). Laboratory test done including Hb level. MIRENA inserted, and ask them to check the Hb after 4 month, after one year and after two year. In each, visit measurement of Hb for this study, in addition to assessment of pattern of bleeding. Women with pathological cause of menorrhagia excluded from this study: Genital tract malignancies, Fibroid, Endometriosis, Blood disease, and thyroid disease. Data analyzed using Statistical Package for Social Sciences (SPSS) version 24, paired t- test performed for differences in level of haemoglobin. Level of statistical significance was set at P value < 0.05.

Results
Current study was done on 30 patients attained the family planning outpatient department of Alkadhmiya Hospital, had abnormal uterine bleeding (AUB), they were aged between 35-46 years. The mean age of the patients was 40.5±3.4 years The mean baseline Hemoglobin (Hb) was 7.6±0.6%, mean Hb after 4 months was 8.5±1.5%, mean Hb after 1 year was 11.2±1.4% and the mean Hb after 2 years was 12.1±0.4%, table(1) show paired t-test to test the significance raise of mean Hb% after 4 months, 1 and 2 years from baseline mean Hb%.
Mean Hb% showed a significant rise from baseline Hb%, $p<0.001$.

Table 1: (paired t-test) Rise of Mean patient's hemoglobin during the study

Mean blood Hb ± SD				P value
Baseline	**After 4 months**	**After 1 year**	**After 2 years**	
7.6±0.6	8.5±1.5	11.2±1.4	12.1±0.4	<0.001

As shown in table (2), mean Hb% showed a significant rise of 5(16.7%) patients after 4 months form baseline Hb%.
Mean Hb% showed a significant rise of 24(80%) patients after 1 year form baseline Hb%.
Mean Hb% showed a significant rise of 30(100%) patients after 2 years form baseline Hb%.

Table 2: Distribution of the patients according to their Hb% measurement's during study

Hb	After 4 months	After 1 year	After 2 years
Normal	5(16.7%)	24(80%)	30(100%)
Low	25(83.3%)	6(20%)	___
Total	30	30	30

All patients presented with menorrhagia, after 4 months the bleeding patterns in all patients was shown in table (3), reduction in menstrual blood loss (MBL) is seen

progressively over a period of 4 months, 1 year, and 2 years. Five (16.7%) patients became amenorrheic after 4 months and 22(73.3%) patients became amenorrheic by the end of 1 year. All women (100%) became amenorrheic at the end of 2 years.

Table 3: Bleeding pattern during the study

Bleeding pattern	At presentation	After 4 months	After 1 year	After 2 years
Amenorrhea	___	5 (16.7%)	22(73.3%)	30(100%)
Spotting	___	21(70%)	6(20%)	___
Moderate bleeding	12(40%)	2(6.7%)	2(6.7%)	___
Heavy bleeding	18(60%)	2(6.7%)	0	___
Total	30	30(100%)	30	30

96.6% patients were satisfied with Mirena insertion.

Some of the patients had comorbidities, five (16.7%) women had hypertension, 3(10%) had diabetes, 2 (6.7%) had both hypertension and diabetes, and two (6.7%) had bronchial asthma, as shown in fig (2).

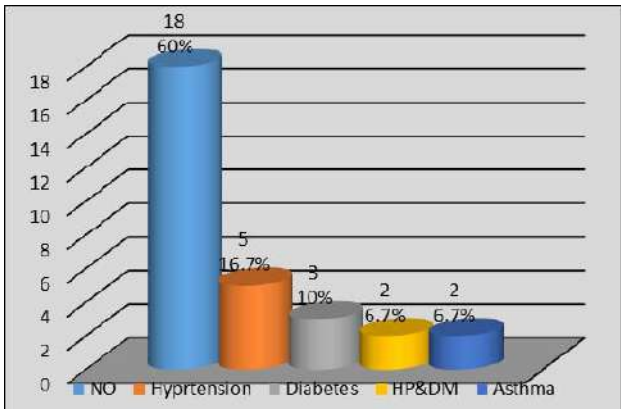

Fig 2: distribution of the patients according their comorbid diseases

Discussion

Abnormal uterine bleeding was high prevalence in women. Heavy bleeding during menstrual cycle is often incapacitating and often leads to anemia if not managed. In the past oral contraceptives and oral progesterone were being used, but now with advent of intrauterine devices and vaginal ring delivery systems the management and compliance has improved [28].

Excessive bleeding results in iron deficiency anemia, which in turn leads to serious medical problems and impacts women's quality of life [29]

Current study showed that Mirena reduced uterine bleeding and increased baseline Hb level (improve anaemia).

The mean Hb after 4 months was 8.5±1.5percentage, after 1 year was 11.2± 1.4% and after 2 years was 12.1± 0.4%.

The mean Hb level improved in 16.7% of patients after 4 months, 80% of the patients after 1 year and in 100% of patients after 2 years form baseline Hb%. This improvement in Hb level mainly because of the effect of Marina in uterine bleeding reduction.

Current study showed that 7% of the patients became amenorrheic after 4 months, 73.3% of the patients became amenorrheic by the end of 1 year. All women (100%) became amenorrheic at the end of 2 years.

Other studies also showed similar result as a significant increase in Hb and improvement of uterine bleeding [28, 30-34].

96.6% patients were satisfied with Mirena insertion. Reasons for disliking were minor side effects as intermittent spotting. However, none of them required removal of Mirena.

As 40% of the patients had comorbid diseases so Mirena had benefit and can used in these patients this result concluded also by Pallavi C et al study[35].

Conclusion

LNG locally released on endometrium cavity is both a safe and reliable method of abnormal uterine bleeding treatment. It benefits from the atrophic effect of progestin on endometrium, while not suffering the systemic side effect seen with other method of progestin administration. Even so, as it cause marked endometrial atrophy leading to menstrual disturbances, hypo menorrhea and amenorrhea. Side effects are generally mild and most of the times assurance is enough to ensure continuation of device.

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