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ORIGINAL ARTICLE

Does Timing of Levonorgestrel Insertion in Women with Abnormal Uterine Bleeding Affect its Expulsion and Bleeding Pattern? A Follow-Up Study

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Abstract

Background Levonorgestrel Intra Uterine System insertion for contraception is preferred in the follicular phase. However, the ideal time of insertion for Abnormal Uterine Bleeding is not stated clearly. The aim of our study is to find out the effect of timing of insertion on expulsion and irregular bleeding pattern post insertion.

Methods A follow-up study of patients with LNG-IUS for AUB was conducted. They were grouped into four based on the day of insertion from Last Menstrual Period (LMP). The pattern of irregular bleeding post insertion was compared with odds ratio and the expulsion rate was compared with log rank test.

Results The most common indication for the 76 patients was ovulatory dysfunction (39.4%) followed by Adenomyosis (36.84%). Those who had LNG-IUS insertion from day 22–30 had quicker expulsions of 25% of patients by 3 months. By 6 months and later expulsion rate was much higher in the luteal phase than the follicular phase ($p < 0.03$). The least risk of moderate or heavy bleeding was for the 8–15 day group when compared to the 22–30 day group, the odds ratio being 0.03 [95% CI: (0.01–0.2)].

Conclusion Based on expulsion rate alone, insertion of LNG-IUS at any time in the follicular phase is ideal. Considering both expulsion rate and pattern of bleeding the ideal time would be late follicular phase, that is 8–15th day.

Keywords Abnormal uterine bleeding (AUB) · Last menstrual period (LMP) · Levonorgestrel intra uterine system (LNG IUS) · Expulsion rate · Follicular phase · Luteal Phase

Introduction

Abnormal uterine bleeding (AUB) is a significant problem among women of reproductive age group affecting 14–25% of women of reproductive age [1]. HMB is often incapacitating and expensive to treat and can severely affect a woman's quality of life both personal as well as social.

The Levonorgestrel Intrauterine System (LNG-IUS) is a boon to many women with AUB as it provides symptomatic relief. It is recommended by NICE and other international guidelines as the first line of treatment for HMB [2, 3]. It is also recommended as first-line medical management of endometrial hyperplasia without atypia [3]. This has led to a decrease in the number of unnecessary hysterectomies since these guidelines were implemented.

Several studies have examined the association of the timing of insertion and expulsion rate of IntraUterine Device (IUD) for contraceptive use with varying definition of time such as phase of menstrual cycle [4] and postpartum [5].

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Although IUD insertion is preferred in the bleeding phase of the menstrual cycle to avoid the risk of concurrent pregnancy, a systematic review of eight studies concluded that the timing of IUD insertion based on phases of a menstrual cycle has little effect on rates of continuation, removal, expulsion, pregnancy, pain at insertion, and bleeding at insertion [4]. Another systematic review in 2018 that examined expulsion in relation to the postpartum period, reported that expulsion was seen in 10% of the women for whom an IUD was inserted within 10 min of placental delivery, 29.7% if done within 4 weeks and 1.95% for insertion done after 4 weeks [5].

However, for AUB the ideal time of insertion is not clear. According to the manufacturer's insertion instructions, the LNG-IUS can be inserted within seven days of the onset of menstruation or immediately after a first-trimester abortion and device replacement can occur at any time during the menstrual cycle (MIRENA/Bayer HealthCare Pharmaceuticals). The manufacturers also suggest that fundal positioning of LNG-IUS is particularly important in order to ensure uniform exposure of the endometrium to the progestogen to prevent expulsion and maximize efficacy. Some of the complications of inserting an IUD are post-insertion pain lasting from 3 days to 6 weeks of insertion and persistent heavy bleeding. This may be a result of either malposition or expulsion of IUD which may be caused by premenstrual cramps and uterine contractions. Although malpositioning can be asymptomatic, it is often associated with pain and bleeding [6]. Hence the purpose of this study is to describe the bleeding patterns and the expulsion rate of LNG-IUS following its insertion and associate the same with various phases of the menstrual cycle.

Materials and Method

This follow-up study was conducted at a tertiary care hospital in Kerala after getting clearance from the Institutional Ethics Committee. It included patients with AUB and a uterine size less than 12 weeks who underwent LNG-IUS (MIRENA) insertion during the period Jan 2020 to March 2022 after getting their informed consent. Women with recent or past Pelvic Inflammatory Disease (within 3 months), submucous fibroid protruding into cavity, bleeding due to coagulopathy, women who are not sure of their Last Menstrual Period (LMP) and those with pipelle-based endometrial biopsy report of atypical hyperplasia or carcinoma endometrium were excluded from the study. Drug-induced AUB was also excluded.

After documenting history and clinical examination, Pap smear was taken followed by transvaginal and abdominal ultrasound. They were classified according to the PALM-COEIN classification. MIRENA (LNG-IUS) was inserted in the Gynaecology OPD after giving oral analgesics 2 h prior to the procedure. Data was retrieved from an electronic database which included LMP, day of insertion from LMP, phase of menstrual cycle, pattern and duration of irregular bleeding following insertion and date of expulsion or partial expulsion if any. Day of insertion from LMP was categorized as: day 1–7, day 8–15, day 16–21 and day 22–30.

They were grouped based on their irregular bleeding pattern following LNG-IUS insertion as follows: those with just spotting per vaginum lasting for less than 1 month; those who used one sanitary pad a day in the last 1 month, categorized as mild bleeding; those using 2–3 pads per day, categorized as moderate bleeding and those who needed more than 4 pads per day or bleeding most of the days a week, categorized as heavy bleeding. Moderate bleeding was further categorised as bleeding less than 2 months and more than 2 months.

The patients were called for a review after 1 month, 2–4 months and 6 months after insertion and thereafter they were followed up by telephone. Those who were not able to come for review were contacted by phone and information regarding irregular bleeding pattern and its duration was taken.

Statistical analysis included descriptive statistics such as frequencies, proportions and means with standard deviation. Association was established using chi-square test, odds ratio with 95% confidence interval and survival analysis including Kaplan Meir Curves and log-rank test was done using SAS-ODA.

Results

Of the 76 patients who met the inclusion and exclusion criteria, the most common indication for MIRENA insertion was AUB-O: Ovulatory dysfunction. That is, 30 (39.5%) had no structural lesion. This was followed by AUB-A: Adenomyosis 28 (36.8%), AUB:-L: fibroid uterus 10 (13.6%) and AUB-M: hyperplasia without atypia 8 (10.5%). See Fig. 1.

As per the pipelle endometrial biopsy report, the majority 29 (38.16%) had secretory endometrium followed by proliferative endometrium in 23 (30.26%), disordered Proliferative Endometrium in 13 (17.1%), hyperplasia without atypia in 8 (10.5%) and hormonally modified endometrium in 3 (4.0%) as they were on progestin for heavy bleeding. See Fig. 2.

On categorizing based on the day of insertion of LNG-IUS after LMP, majority of insertions [31 (40.8%)] were done between 8 and 15th day. The remaining were almost equally distributed across the other phases. See Table 1.

The expulsion rate (expelled or removed as it was displaced resulting in heavy bleeding) in this study population was 17.1% (13 cases). Out of 13, 7 (53.8%) of them had adenomyosis (AUB-A), 3 (23.1%) had fibroid uterus

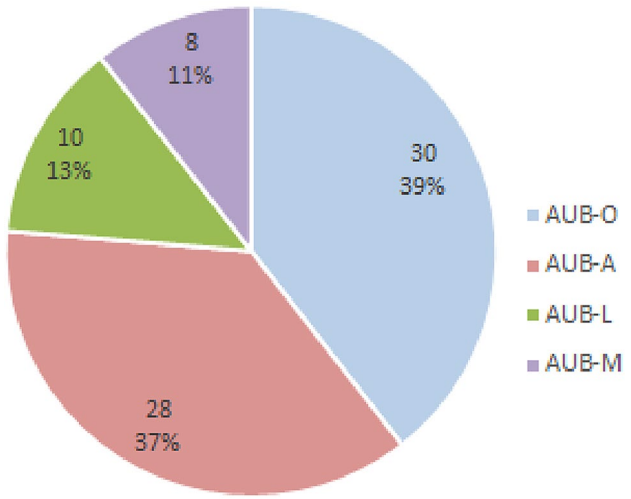
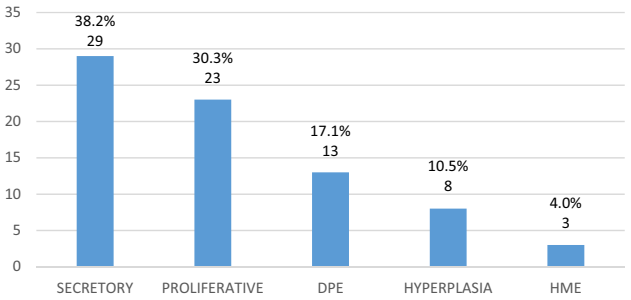


Fig. 1 Indication for LNG-IUS



*DPE - Disordered Proliferative Endometrium,
HME - Hormonally Modified Endometrium

Fig. 2 Distribution based on Pipelle biopsy report

(AUB-L) and the remaining 3(23.1%) had ovulatory dysfunction (AUB-O). The highest expulsion rate was 37.5% (6 cases) among those for whom the insertion was between 22nd and 30th day, followed by 21.4% (3 cases) among those who had the insertion between 16th and 21st day, 9.7% (3 cases) among those who had insertion between 8 and 15th day and 6.7% (1 case) among those who had insertion between 0 and 7th day. There was no significant difference between the 2 weeks in the follicular phase ($p=0.7$) nor between the two weeks in the luteal phase ($p=0.3$). However, the rate of expulsion between the follicular phase and the luteal phase was significantly different ($p=0.02$). See Table 1.

The patients were followed up for a maximum period of 26 months with a mean (±SD) follow-up period of 12.8 (±8.1) months, the range being 5 days to 27.1 months. As shown in the Kaplan Meier Curve (Fig. 3), by 3 months about 25% of those who had an LNG-IUS inserted between 22nd and 30th day had an expulsion or partial expulsion but only about 7% for each of the other groups. By 6 months 32% of those with insertion between 22nd and 30th and 24% of those with insertion between 16th and 21st day had expulsion and the other 2 groups still had only about 6.5% expulsion. By 1 year 42% of those who had an insertion between 22nd and 30th day had expulsion and those who had an insertion between 8 and 15th day had expulsion rate of 10%. The other two groups remained the same. The overall expulsion-free rates were significantly different ($p=0.03$) across the various groups using the Log Rank test. However, the rates were not different between the two groups of the follicular phase ($p=0.8$) and between the two groups of the luteal phase ($p=0.3$).

The comparison of the day of insertion to the pattern of bleeding is shown in Fig. 4. Heavy bleeding was present only in 6.5% when the insertion time was between 8 and 15th day. This was similar when insertion was done between 0 and 7th day: 6.7% ($p=0.97$) and 16th–21st day: 7.1% ($p=0.93$). However, this was significantly different when insertion was between 22nd and 30th day: 43.8% ($p=0.002$). Majority of the patients in the 8th–15th day group had only spotting post insertion (54.8%) followed by mild bleeding (25.8%) and had lesser occurrences of persistent bleeding. This pattern was similar in the 0–7th day group with 60.0% for the two patterns combined ($p=0.16$) but significantly different from 16th and 21st day with 50% ($p=0.04$) and significantly different from 22nd to 30th day with 12.5% ($p<0.00001$). Proportion of occurrence of moderate to heavy bleeding post insertion between follicular phase (group 1 and group 2) and luteal phase insertion (group 3 and group 4) was significantly different ($p=0.0002$) based on chi-square test. That is, post insertion bleeding was significantly less if insertion was done during the follicular phase.

The association between pattern of bleeding and day of insertion is better portrayed in Table 2. The odds of

Table 1 Association of day of insertion of LNG-IUS and expulsion rate

Phase	Day of insertion	Total	Expulsion	*p*-value	Overall *p* value
Follicular	0–7th Day	15 (19.7%)	1 (6.7%)	0.73	0.02
	8–15th Day	31 (40.8%)	3 (9.7%)		
Luteal	16–21st Day	14 (18.4%)	3 (21.4%)	0.34	
	22nd–30th Day	16 (21.1%)	6 (37.5%)		
	Total	76	13 (17.1%)		

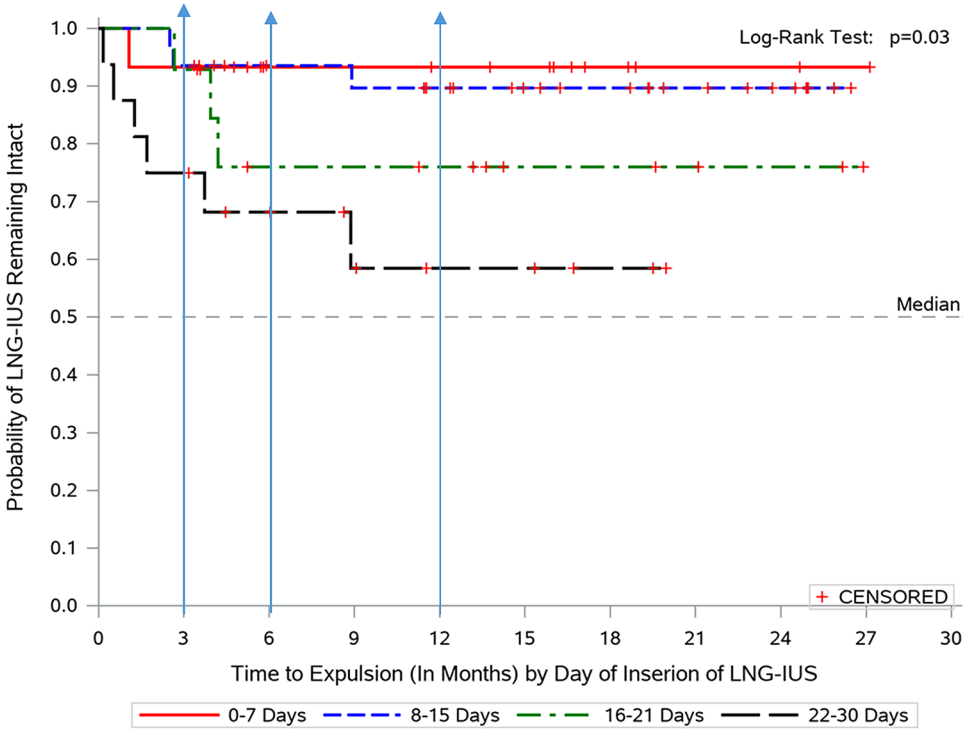


Fig. 3 Time to expulsion by day of Insertion of LNG-IUS

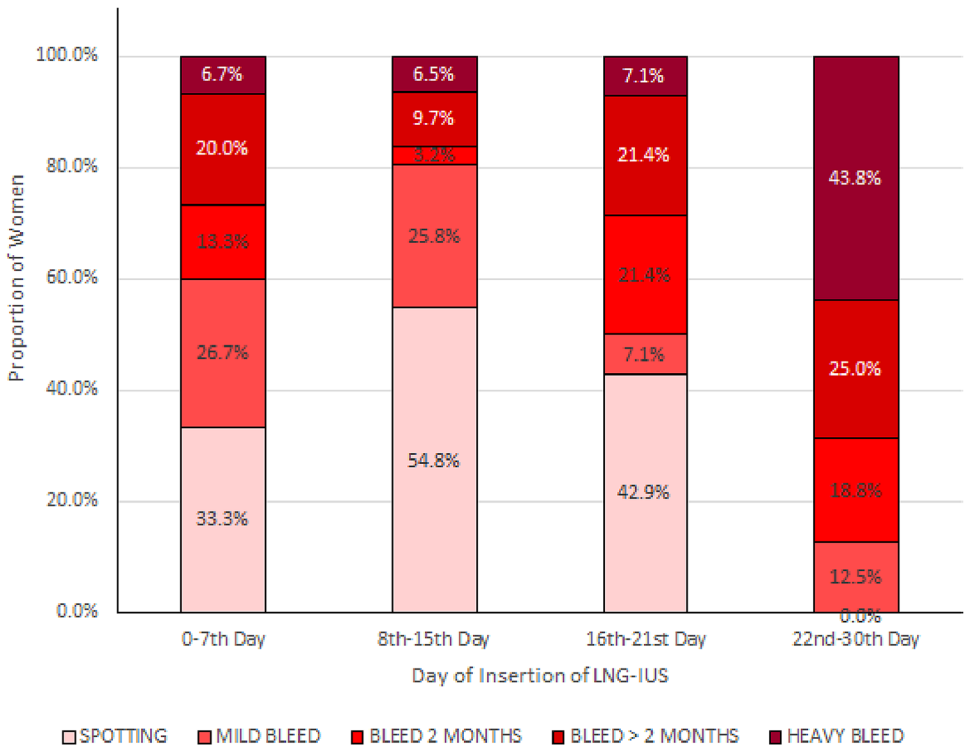


Fig. 4 Distribution of the pattern of bleeding by the day of insertion

developing moderate or heavy bleeding is 0.10 [95% CI: (0.02–0.6)] when the insertion of LNG-IUS is between 0 and 7th day, 0.03 [95% CI: (0.01–0.2)] when it is between 8 and 15th day and 0.14 [95% CI: (0.02–0.9)] when it is between 16th and 21st day as compared to when it is between 22nd and 30th day. The least risk of developing moderate or heavy bleeding is therefore days 8–15.

Table 2 Association of the time insertion of LNG-IUS and pattern of bleeding

Day of insertion	Total	Moderate + Heavy	Spotting + Mild	OR (95% CI)
0–7th day	15 (19.7%)	6 (18.2%)	9 (20.9%)	0.10 (0.02–0.6)
8–15th day	31 (40.8%)	6 (18.2%)	25 (58.1%)	0.03 (0.01–0.2)
16–21st day	14 (18.4%)	7 (21.2%)	7 (16.3%)	0.14 (0.02–0.9)
22nd–30th day	16 (21.1%)	14 (42.4%)	2 (4.7%)	1.0 (Reference)
Total	76	33	43	

Discussion

LNG-IUS is now a well-accepted tool for AUB. Our study showed that AUB-O was the most common indication (39.4%) followed by Adenomyosis (36.8%). This is similar to a study by Dhamangaonkar et al. [7] who reported that 37% of MIRENA users had Adenomyosis. Many patients with adenomyosis prefer hysterectomy for symptom relief. However, several studies have shown that LNG-IUS is extremely effective in resolving AUB and reducing uterine volume in a long-term management plan [8]. It is also effective for AUB due to leiomyoma Uterus [9]. Tabulation of pipelle biopsy report showed secretory (38.16%) followed by proliferative endometrium as the most common finding (30.26%). A study by Ilavarasi CR et al. [10] in 2015 also reported incidence of 30.2% for proliferative endometrium.

The aim of this study was to find the most suitable time for LNG-IUS insertion. The optimum time of insertion recommended for contraceptive purposes is within 7 days of LMP. However, equivalent information for AUB is not available [4]. We, therefore, grouped the day of insertion into 4 groups. The four groups were followed up and it was observed that insertion during day 22–30 had the maximum number of expulsions (Table 1). Based on the Kaplan Meier curves the expulsion rate in this group was found to be 42% by 1 year. The other three groups had only 10% or less (Fig. 3).

Intrauterine pressure is expected to be highest in the late luteal phase of the cycle and lowest in the early follicular phase as per one study which measured intrauterine pressure in the non-pregnant uterus [11]. Therefore, our study finding of significantly higher expulsion rate during the luteal phase is consistent with this mechanism. Unlike the recent study that showed maximum expulsion during early follicular phase [12].

Spotting and mild bleeding per vaginum are expected following LNG-IUS insertion and all patients are counselled about it prior to insertion. The fundal placement of the device is recommended for optimal efficacy. Malposition of LNG-IUS can present with irregular bleeding and pain post insertion [13]. An early analysis of study by Shimoni et al. [14] showed there was lesser bleeding during insertion in the follicular phase compared with luteal phase insertion but this was not statistically significant in later analysis. In our study, majority of those for whom the insertion was done between 8 and 15th day had only spotting or mild bleeding. However, all patients who had insertion between 22nd and 30th day had irregular bleeding and up to 44% had heavy bleeding. As shown in Table 2, the odds of moderate or heavy bleeding are the least for the late follicular phase, followed by early follicular phase and early luteal phase when compared to the late luteal phase which had the highest odds of moderate or heavy bleeding. This is probably due to the higher intrauterine pressure during the luteal phase leading to displacement (Partial expulsion) of LNG-IUS.

Conclusions

Insertion of LNG-IUS for AUB is recommended in the follicular phase (0–15 days from LMP) because the expulsion rate and post-insertion heavy bleeding is highest in the luteal phase. Considering the 2 time periods 0–7 days and 8–15 days, both have a similar expulsion rate but post insertion persistent bleeding PV is found to be higher in the first group. Hence 8–15th day from LMP would be the ideal time for LNG-IUS insertion for women with Abnormal Uterine Bleeding.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest associated with this manuscript.

Ethical Approval Ethical approval was obtained from the Institutional Ethics Committee of Believers Church Medical College, Thiruvalla, Kerala.

Ethical Standard The study was conducted in accordance with the ethical standards of our Institutional Ethics and Research Committee and with 1964 declaration of Helsinki and its amendments.

Informed Consent Informed consent was taken from all participants at the beginning of study.

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