Expulsion of a Levonorgestrel-releasing Intrauterine System: a Retrospective Analysis

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Objective: To report the incidence of expulsion of a levonorgestrel-releasing intrauterine system (LNG-IUS) in Chinese patients and to determine the associated risk factors.
Methods: Medical records of patients who underwent insertion of a LNG-IUS between 1 November 2008 and 31 January 2017 at Tuen Mun Hospital were reviewed. The primary outcome was complete or partial expulsion of the device. Patients with or without expulsion were compared to determine the associated risk factors.
Results: A total of 185 patients (mean age, 44 years) with 263 episodes of LNG-IUS insertion were analysed. The mean follow-up was 38.49 (range, 3-113) months; 84.8% of patients were parous. The most common indication for insertion was menorrhagia (73.4%), followed by endometrial hyperplasia without atypia (24%), and endometrial hyperplasia with atypia (3%). The expulsion rate was 35% (n=92); 76 were complete and 16 were partial. 84.8% of expulsions occurred within the first year of insertion; the median time to expulsion was 4 (range, 1-53) months. Compared with patients without expulsion, those with expulsion were more likely to be parous (91.3% vs. 81.3%, p=0.031), have an abdominally palpable uterus (10.9% vs. 4.1%, p=0.033), a longer uterine cavity (8.51 vs. 8.04 cm, p=0.001), fibroids (44.6% vs. 29.8%, p=0.017), adenomyosis (23.9% vs. 11.1%, p=0.006), and the indication for insertion being menorrhagia (94.6% vs. 62%, p<0.001) or dysmenorrhoea (29.3% vs. 12.9%, p=0.001). In multivariable analysis, risk factors for expulsion were an abdominally palpable uterus (adjusted hazard ratio=2.01, p=0.04), menorrhagia (adjusted hazard ratio=6.59, p<0.001), and dysmenorrhoea (adjusted hazard ratio=1.96, p=0.005). 27 patients underwent reinsertion of a LNG-IUS after expulsion; 13 (48.1%) of whom experienced re-expulsion.
Conclusion: Patients with menorrhagia and dysmenorrhoea are at higher risk of expulsion of LNG-IUS. To reduce the risk of expulsion, the LNG-IUS should be inserted during the later part of the menstrual cycle after pregnancy has been excluded. For patients with an abdominally palpable uterus, the LNG-IUS may not be suitable as the first-line management for menorrhagia or dysmenorrhoea owing to the high risk of expulsion; detailed counselling and frequent follow-up should be provided.

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Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an effective long-acting reversible contraceptive device that releases 20 micrograms of levonogestrel in utero every day[1]. It is recommended by the National Institute for Health and Care Excellence as the first-line management for menorrhagia[2]. The Royal College of Obstetricians and Gynaecologists and Hong Kong College of Obstetricians and Gynaecologists also recommend LNG-IUS as the first-line management for endometrial hyperplasia without atypia[3,4].

Expulsion of a LNG-IUS has been reported to occur in <1 in 20 women over a five-year period[1,2]. When expulsion occurs, women may fall pregnant, treatment for menorrhagia may fail with consequent anaemia, and endometrial hyperplasia may progress to endometrial carcinoma[5]. This study aimed to report the incidence of expulsion of a LNG-IUS in Chinese patients and to determine the associated risk factors.

Materials and Methods

This retrospective study was approved by the New Territories West Cluster Research Ethics Committee (Reference: 18028). Medical records of patients who underwent insertion of a LNG-IUS between 1 November 2008 and 31 January 2017 at Tuen Mun Hospital were

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reviewed. Some patients underwent repeat insertions; each episode was counted as a separate case. Patients were excluded if they were lost to follow-up within one year of insertion or if the LNG-IUS was removed within one year of insertion.

Patient characteristics including age at insertion, parity, size of uterus, length of uterine cavity, and indication for LNG-IUS insertion were collected, as were ultrasonographic findings of adenomyosis and fibroids. The primary outcome was complete or partial expulsion of the LNG-IUS. Complete expulsion was either reported by the patient or confirmed by ultrasonography or pelvic radiography after a report of a missed thread on speculum examination or incidental finding. Partial expulsion was defined as a part of the LNG-IUS visible during a speculum examination. Displacement of the LNG-IUS to the lower cavity or endocervical canal was not considered expulsion. Such patients underwent early removal and were excluded from analysis.

Patients with or without expulsion were compared using the Student's *t* test for continuous variables and the Chi squared test for nominal data. Cox regression analysis was performed; variables with a p value of <0.1 or with clinical significance were further analysed in the multivariable analysis. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 21.0; IBM Corp, Armonk [NY], US).

Results

A total of 245 patients with 323 episodes of LNG-IUS insertion were identified. 12 patients were lost to follow-up within one year of insertion and 48 patients discontinued within one year owing to acute pelvic inflammatory disease / tubo-ovarian abscess (n=3), hysterectomy as definitive treatment (n=4), newly diagnosed breast cancer (n=1), request for early removal secondary to spotting (n=4) or planning conception (n=1), removal of a displaced LNG-IUS (n=7), or endometrial assessment (n=28). The remaining 185 patients (mean age, 44 years) with 263 episodes of LNG-IUS insertion were analysed (Figure 1). The mean follow-up was 38.49 (range, 3-113) months; 84.8% of patients were parous. The most common indication for insertion was menorrhagia (73.4%), followed by endometrial hyperplasia without atypia (24%), and endometrial hyperplasia with atypia (3%).

The expulsion rate was 35% (n=92); 76 were complete and 16 were partial. 84.8% of expulsions occurred within the first year of insertion; the median time to expulsion was 4 (range, 1-53) months. Compared with patients without expulsion, those with expulsion were more likely to be parous (91.3% vs. 81.3%, p=0.031), have an abdominally palpable uterus (10.9% vs. 4.1%, p=0.033), a longer uterine cavity (8.51 vs. 8.04 cm, p=0.001), fibroids (44.6% vs. 29.8%, p=0.017), adenomyosis (23.9% vs. 11.1%, p=0.006), and the indication for insertion being menorrhagia (94.6% vs. 62%, p<0.001) and/or dysmenorrhoea (29.3% vs. 12.9%, p=0.001) [Table 1].

In multivariable analysis, risk factors for expulsion were an abdominally palpable uterus (adjusted hazard ratio=2.01, p=0.04), menorrhagia (adjusted hazard ratio=6.59, p<0.001), and dysmenorrhoea (adjusted hazard ratio=1.96, p=0.005) [Table 2]. The cumulative probability of the LNG-IUS remaining in situ over 5 years stratified with menorrhagia and dysmenorrhoea are shown in Table 3 and Figure 2.

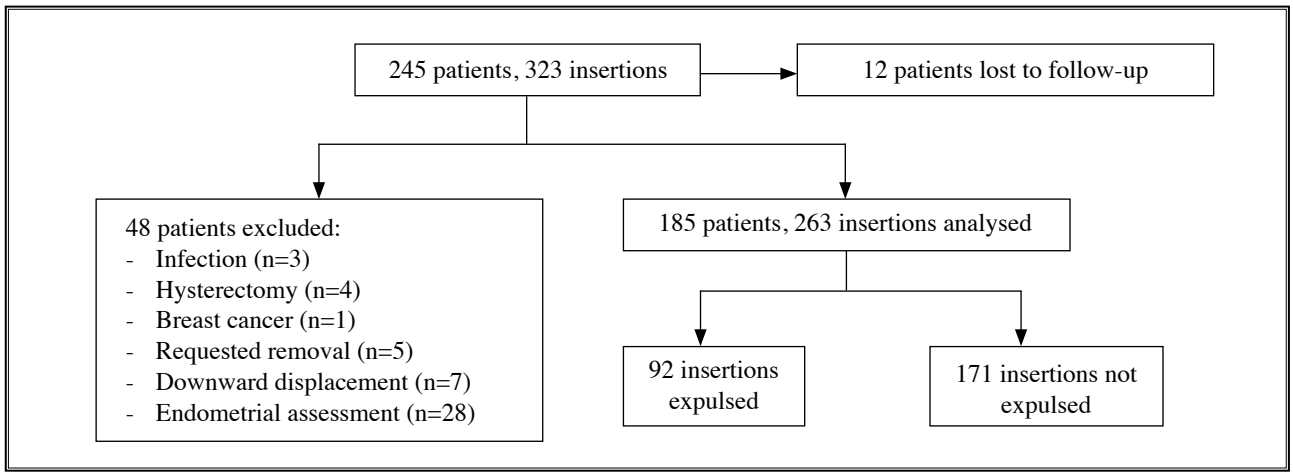

Figure 1. Flowchart of patients who underwent insertion of the levonorgestrel-releasing intrauterine system

Table 1. Patient characteristics

Characteristic	Expulsion		p Value
	No (n=171)*	Yes (n=92)*	
Age of insertion, y	43.63 ± 6.88	44.79 ± 5.57	0.16
Parity			0.031
0	32 (18.7)	8 (8.7)	
≥1	139 (81.3)	84 (91.3)	
Abdominally palpable uterus			0.033
No	164 (95.9)	82 (89.1)	
Yes	7 (4.1)	10 (10.9)	
Uterine cavity length, cm	8.04 ± 0.91	8.51 ± 1.11	0.001
Fibroids			0.017
No	120 (70.2)	51 (55.4)	
Yes	51 (29.8)	41 (44.6)	
Adenomyosis			0.006
No	152 (88.9)	70 (76.1)	
Yes	19 (11.1)	22 (23.9)	
Indication for insertion			
Menorrhagia			<0.001
No	65 (38)	5 (5.4)	
Yes	106 (62)	87 (94.6)	
Dysmenorrhoea			0.001
No	149 (87.1)	65 (70.7)	
Yes	22 (12.9)	27 (29.3)	
Endometrial hyperplasia without atypia			0.002
No	120 (70.2)	80 (87)	
Yes	51 (29.8)	12 (13)	
Endometrial hyperplasia with atypia			0.176
No	164 (95.9)	91 (98.9)	
Yes	7 (4.1)	1 (1.1)	
History of expulsion			0.13
No	157 (91.8)	79 (85.9)	
Yes	14 (8.2)	13 (14.1)	
Duration of usage, m	29.53 ± 18.59; 21 (12-88)	7.20 ± 10.04; 4 (1-53)	<0.001
Follow-up, m	38.74 ± 27.83; 24 (12-113)	38.01 ± 25.91; 33 (3-111)	0.84

* Data are presented as mean ± standard deviation, No. (%) of cases, or mean ± standard deviation; median (range)

Table 2. Risk factors for expulsion using the Cox regression model

Variable	Adjusted hazard ratio (95% confidence interval)	p Value
Parity ≥1	1.06 (0.50-2.24)	0.91
Abdominally palpable uterus	2.01 (1.02-3.95)	0.04
Menorrhagia	6.59 (2.57-16.90)	<0.001
Dysmenorrhoea	1.96 (1.23-3.12)	0.005
Endometrial hyperplasia without atypia	0.94 (0.50-1.77)	0.85

Table 3. Cumulative rate of expulsion

Parameter	Time after insertion			
	1 month	6 months	12 months	>12 months
Cumulative No. (%) of expulsions (n=92)	31 (33.7)	61 (66.3)	74 (81.5)	92 (100)
Cumulative rate of expulsion of cohort (n=263), %	11.8	23.2	28.1	35.0

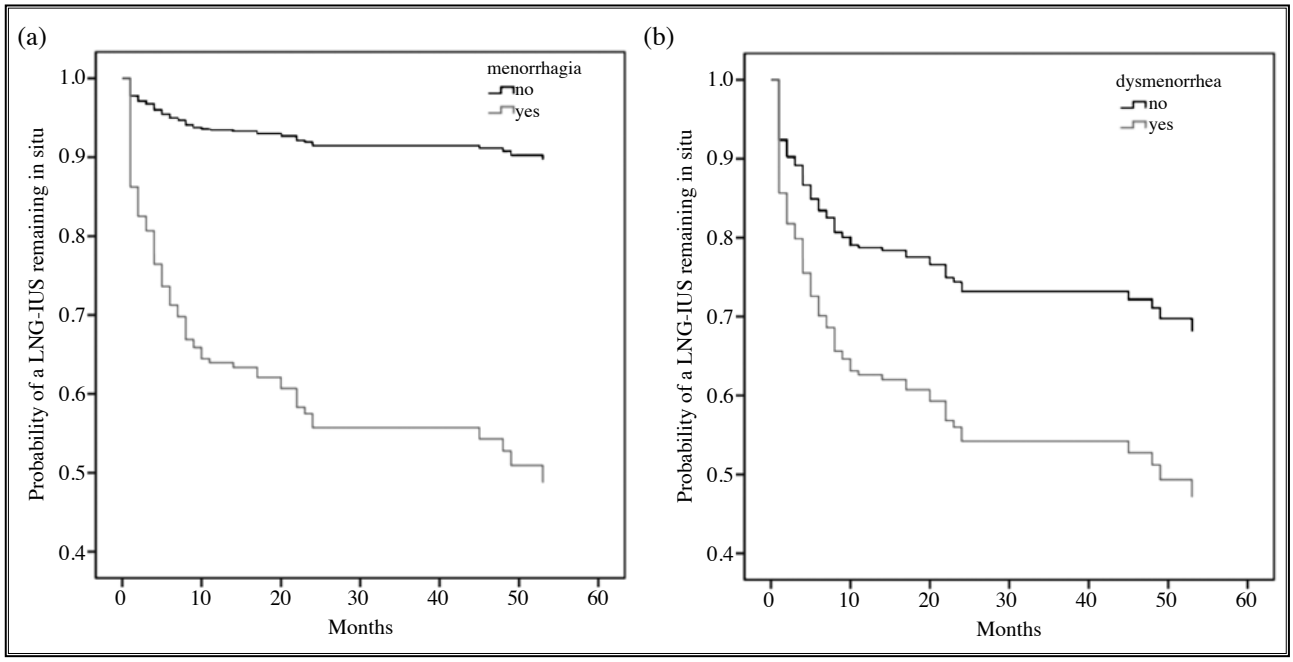

Figure 2. Cumulative probability of the levonorgestrel-releasing intrauterine system (LNG-IUS) remaining in situ stratified by (a) menorrhagia and (b) dysmenorrhoea

27 patients underwent reinsertion of a LNG-IUS after expulsion; 13 (48.1%) of whom experienced re-expulsion. The median interval to expulsion was 4 (range, 1-53) months for the first insertion and 2.5 (range, 1-33) months for the second insertion (p=0.86, paired sample t-test).

Discussion

The LNG-IUS is an effective long-acting device used in the management of menorrhagia and dysmenorrhoea[6]. LNG-IUS usage has been reported to increase haemoglobin level in patients with menorrhagia[7,8]. The prevalence of endometrial hyperplasia further expands the use of LNG-IUS[9]. If endometrial hyperplasia persists after 12 months of LNG-IUS use, hysterectomy should be discussed. Expulsion of LNG-IUS is a known complication and mostly occurs within the first year of insertion[10].

The mean age of our patients was 44.03 years, which was older than that reported in most studies. In our patients, LNG-IUS was used mainly for treatment of gynaecological problems (menorrhagia, dysmenorrhoea, and endometrial hyperplasia) rather than contraception.

According to the manufacturer and National Institute for Health and Care Excellence guideline, the risk of expulsion of a LNG-IUS is <5%[1,2]. This expulsion rate has been further reported to range from 5.7% in 5 years to 25.3% in 2 years[7,11-18]. In our study, the expulsion rate was much higher at 28.1% in the first year and 35% cumulatively. Nonetheless, most studies on the expulsion rate of the copper intrauterine device (IUD) and LNG-IUS have focused on patients whose primary indication was contraception. In contrast, none of our patients used the LNG-IUS solely for contraception; most had menorrhagia or dysmenorrhoea, and both are significant risk factors for expulsion[16,19-21]. The expulsion rate has been reported to be higher for LNG-IUS than IUD[16,17], probably because of increased menstrual flow in LNG-IUS patients; most patients reported expulsion during heavy menses. In

our patients, most of the LNG-IUS were inserted during admission for heavy menstrual flow; 31 (33.7%) expulsions occurred within 1 month of insertion. In a study that involved over 9000 women in Portland, the expulsion rate decreased if the IUD was inserted later in the menstrual cycle[22]. The LNG-IUS may be flushed out by heavy menses before levonorgestrel has had an adequate effect on the endometrium. In addition, the expulsion rate in other studies may have been underestimated, as most studies did not clearly define expulsion[7,11,12,14-18] or include partial expulsion[7,12,14-18]. One study relied only on patient reporting of expulsion that can be easily missed[15]. There were only a few studies of expulsion of a LNG-IUS in Chinese patients. A study in Taiwan of patients with adenomyosis reported the highest expulsion rate compared with studies among Caucasian populations[16]. Regional/ethnic differences in the expulsion rate have been reported in a multi-centre study[12]. Further study with a larger sample size is required to determine the expulsion rate in our local population with menorrhagia or dysmenorrhoea.

Adenomyosis and dysmenorrhoea increase the risk of expulsion[16,19,21]. Dysmenorrhoea is associated with increased prostaglandins in the uterus that increase the contractile force of the uterus and hence the chance of expulsion of a LNG-IUS[23]. Menorrhagia and dysmenorrhoea are common indications for LNG-IUS insertion. Despite the increased risk of expulsion, the use of LNG-IUS is still recommended, and can result in an increase in haemoglobin level by 1.17-1.8 g/dl[6-8]. LNG-IUS is also suitable for patients who opt for conservative treatment or while awaiting surgery. It is important to explain the risk of expulsion. Patients should be taught to self-check the thread regularly and attend follow-up to ensure appropriate management if the LNG-IUS is expulsed.

The manufacturer recommends the use of LNG-IUS on the uterus sounded to 6 to 10 cm[1]. Within this range, the uterine cavity length does not affect the risk of expulsion[19,24]. The risk of expulsion increases if the uterus is too large with a consequent higher chance of malposition of the LNG-IUS. Such patients should be counselled about the higher risk of expulsion and that the LNG-IUS may not be an appropriate first-line management for menorrhagia or dysmenorrhoea.

In case of expulsion, immediate reinsertion of a new LNG-IUS is advised after pregnancy has been excluded. About 34% of patients experience re-expulsion after the first IUD expulsion; the risk is much higher if the first expulsion occurred within 3 months of insertion[25]. In our study, 48.1% of patients had re-expulsion after reinsertion. Nonetheless, a history of expulsion was not a risk factor for expulsion. This may be due to the small number of patients who underwent reinsertion.

One limitation of this study was its retrospective nature. 28 patients with early removal of LNG-IUS for endometrial assessment were excluded; previous practice in our unit was to remove the copper IUD or LNG-IUS prior to endometrial assessment. Patients with a LNG-IUS in a stable condition were followed up in primary care centres; some of them may have already been transferred before expulsion occurred. Nonetheless, only 4.9% of patients were lost to follow-up and missing data were minimal. Our patients had a high continuation rate of LNG-IUS. Only 2.1% of patients requested early removal, compared with a discontinuation rate of 18% in the first year in one study[11]. With adequate counselling about adverse effects, a higher continuation rate of LNG-IUS for treatment of gynaecological conditions may be assured. The Cox regression model was used for multivariable analysis because expulsion could occur after premature removal.

Conclusion

Patients with menorrhagia and dysmenorrhoea are at higher risk of expulsion of LNG-IUS. To reduce the risk of expulsion, the LNG-IUS should be inserted during the later part of the menstrual cycle after pregnancy has been excluded. For patients with an abdominally palpable uterus, the LNG-IUS may not be suitable as the first-line management for menorrhagia or dysmenorrhoea owing to the high risk of expulsion; detailed counselling and frequent follow-up should be provided.

Declaration

The authors have no conflicts of interest to disclose.

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