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**Comparison of the efficacy of oral contraceptives and levonorgestrel intrauterine system in intermenstrual bleeding caused by uterine niche**

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**ABSTRACT**

This study aimed to compare the effectiveness of oral contraceptives and a levonorgestrel intrauterine system in treating intermenstrual bleeding due to uterine niche. We retrospectively analyzed 72 patients with intermenstrual bleeding due to uterine niche from January 2017 to December 2021, of whom 41 were treated with oral contraceptives and 31 with a levonorgestrel intrauterine system. Post-treatment follow-ups at 1, 3, and 6 months were conducted to compare the efficiency and adverse effects between the two groups. In the oral contraceptive group, the effectiveness rate was higher than 80% at 1-

and 3-months post-treatment and higher than 90% at 6 months. In the levonorgestrel intrauterine system group, the effectiveness rates were 58.06%, 54.84%, and 61.29% at 1, 3, and 6 months of treatment, respectively. Oral contraceptives were more effective than the levonorgestrel intrauterine system in treating intermenstrual bleeding caused by uterine niche ( $p < 0.05$ ).

**Key words:** efficiency; intermenstrual bleeding; levonorgestrel intrauterine system; oral contraceptives; uterine niche

## INTRODUCTION

The incidence of uterine niche increases with an increase in the rate of cesarean deliveries. At 6 weeks postpartum, the incidence of uterine niche in women who delivered via cesarean section was reported to be 43.4% on vaginal ultrasound [1]. Hysteroscopy revealed uterine niche in 75% of women with cesarean delivery[2]. Symptoms of uterine niche include abnormal uterine bleeding, pelvic pain, infertility, and cesarean scar pregnancy [3], which can seriously affect a woman's quality of life and even endanger her life. For women who do not intend to have children, abnormal uterine bleeding is a major disturbance.

Intermenstrual bleeding after cesarean delivery is closely associated with uterine niche. Antila RM [4] explored the relationship between uterine niche and abnormal uterine bleeding one year after cesarean section and suggested that intermenstrual bleeding was associated with uterine niche. Another study found abnormal vaginal bleeding in 30% of women with uterine niche 6 months after cesarean delivery [5]. The mechanism of intermenstrual bleeding caused by uterine niche is unclear. It may be due to anatomical defects resulting in menstrual blood being trapped in the diverticulum or reduced contractile function at the scar site, which may lead to blood accumulation [6]. Additionally, local vascularization of the scar may cause increased intermenstrual bleeding [7].

Women without reproductive requirements seek reliable conservative treatment for intermenstrual bleeding. Hormone therapy for uterine niche is a reasonable treatment

option for women without contraindications [8]. Recent studies have concluded that a levonorgestrel intrauterine system (LNG-IUS) is an effective treatment modality for intermenstrual bleeding associated with uterine niche [9, 10]. Another study concluded that LNG-IUS did not affect the length of menstruation because spotting is a common adverse effect of LNG-IUS, making it difficult to distinguish whether LNG-IUS effectiveness in the treatment of uterine niche. At the same time, oral contraceptives (OC) can shorten the length of menstruation and is an accepted treatment [11]. This study retrospectively analyzed patients with uterine niche with intermenstrual bleeding in the last 5 years to compare the efficacy of OC and LNG-IUS as treatment options.

### **Impact statement**

Intermenstrual bleeding after cesarean delivery is closely associated with uterine niche. Recent studies have concluded that a LNG-IUS is an effective treatment modality for intermenstrual bleeding associated with uterine niche. At the same time, OC can shorten the length of menstruation and is an accepted treatment. This study retrospectively analyzed patients with uterine niche with intermenstrual bleeding in the last 5 years to compare the efficacy of OC and LNG-IUS as treatment options. The results found that in the OC group, the effectiveness rate was higher than 80% at 1- and 3-months post-treatment and higher than 90% at 6 months. In the LNG-IUS group, the effectiveness rates were 58.06%, 54.84%, and 61.29% at 1, 3, and 6 months of treatment, respectively. This study demonstrated that OC was superior to an LNG-IUS in managing intermenstrual bleeding in uterine niche. The outcome may have been influenced by the side effects of spot bleeding associated with an LNG-IUS and needs to be confirmed by a larger sample and longer follow-up.

### **MATERIAL AND METHODS**

This retrospective study included patients with uterine niche who presented at the Fourth Affiliated Hospital of Guangxi Medical University between January 2017 and December 2021 with intermenstrual bleeding for a period of more than 7 days. All

patients were fully informed of the benefits, potential risks, and treatment outcomes and signed consent forms before the procedure and prior to treatment. With the patient's consent, we retrospectively collected the patient's medical records through the electronic medical record system. All patients underwent hysteroscopy (Fig. 1) and endometrial biopsy before receiving the OC or LNG-IUS treatment. The exclusion criteria included endometrial pathology of atypical endometrial hyperplasia or malignancy, contraindication to hormonal therapy, and intermenstrual bleeding resulting from other causes. The study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Guangxi Medical University, and all treatments were performed with patient consent (No. LW2022046).

Before treatment, the patient's age, body mass index (BMI), gravidity, parity, number of cesarean deliveries, history of previous abortions, time of symptom onset from the last cesarean delivery, uterine position, cycle length, and duration of menstruation were recorded. The length, width, and height of the niche and residual myometrium thickness were measured using a transvaginal ultrasound.

Patients in the OC group were administered a daily dose containing 0.03 mg of Ethinyl estradiol and 3 mg of drospirenone for 21 days, starting on the third day of menstruation. The LNG-IUS group (20 ug/d) had the device placed on the third day of menstruation. Patients received follow-ups 1, 3, and 6 months after treatment.

We classified patients' menstrual periods into a group where duration decreased to less than 7 days, a group with periods greater than 7 days but decreased by more than 3 days and a group with no significant change or decrease of fewer than 3 days. The first two were considered valid [12]. Adverse effects were also documented, including amenorrhea, breast tenderness, increased vaginal discharge, pelvic pain, irregular vaginal bleeding, and low libido. Irregular vaginal bleeding is not continuous, distinguishing it from intermenstrual bleeding, whereas amenorrhea is the absence of menstruation for more than three cycles.

## **Statistical analysis**

Statistical Package for the Social Sciences (SPSS) (version 23.0; IBM, Armonk, NY, USA) was used to analyze the data. Proportions and means  $\pm$  standard deviation was calculated. Data were compared using the chi-squared test or t-test.  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 72 patients with uterine niche and intermenstrual bleeding were included, 41 of whom were treated using OC and 31 using LNG-IUS. There were no significant differences in age, BMI, gravidity, parity, previous abortions, number of cesarean deliveries, time of symptom onset from last cesarean delivery, niche volume, residual myometrium thickness, cycle length, duration of menstruation, and uterine position ( $p > 0.05$ ) (Tab. 1).

One month after treatment, OC was seen to be effective in 33 patients (80.49%), of which 20 (48.87%) had their period duration shortened to less than 7 days. Of those patients, 13 (31.71%) still had periods greater than 7 days but decreased by more than 3 days, and 8 (19.51%) had ineffective treatment. In the LNG-IUS group, treatment was effective in 18 patients (58.06%), with period duration shortened to less than 7 days in 14 patients (45.16%), greater than 7 days but shortened by more than 3 days in 4 cases (12.90%), and ineffective in 13 patients (41.94%). Therefore, based on the results from both groups, OC was more effective than LNG-IUS ( $p = 0.038$ ). Three months after treatment, 34 patients (82.93%) in the OC group were treated effectively, of which 22 (53.66%) had periods lasting less than 7 days, 12 patients (29.27%) still had periods greater than 7 days but shortened by more than 3 days, and 7 patients (17.07%) were treated ineffectively. Treatment was effective in 17 cases (54.84%) in the LNG-IUS group, of which 15 cases (48.39%) had periods lasting less than 7 days, 2 cases (6.45%) still had periods greater than 7 days but shortened by more than 3 days, and 14 cases (45.16%) had ineffective treatment. Treatment in the OC group was more effective than in the LNG-IUS group ( $p = 0.009$ ). Six months after treatment, 38 patients (92.68%) in the OC group were treated effectively, of which 28 cases (73.08%) had periods lasting less

than 7 days, 10 cases (19.23%) still had periods greater than 7 days but decreased by more than 3 days, and 3 cases (7.32%) were treated ineffectively. Nineteen cases (61.29%) in the LNG-IUS group were effective; all had periods of less than 7 days, and 12 cases (38.71%) were ineffective. Based on the results obtained, treatment in the OC group was more effective than the LNG-IUS group ( $p = 0.001$ ) (Tab. 2).

The main adverse effects in the OC group were nausea, breast tenderness, and decreased libido. However, nausea decreased gradually with increasing treatment duration, while low libido increased with increasing treatment duration. The main adverse effects observed in the LNG-IUS group were amenorrhea, irregular vaginal bleeding, and increased vaginal discharge (Tab. 3).

## **DISCUSSION**

Uterine niche is defined as a defect at least 2.0 mm deep at the site of a cesarean section scar [13]. Uterine niche can cause a range of symptoms, including abnormal uterine bleeding, infertility, pelvic pain, and cesarean scar pregnancy. Laparoscopy and hysteroscopy are effective treatment options for women with fertility requirements [14]. For women with fertility desire, laparoscopic correction of the isthmocele can increase myometrium thickness [15]. Transvaginal repair has comparable postoperative pregnancy rates to laparoscopic repair, but it is more economical and convenient [16, 17]. Therefore, laparoscopy, vaginal surgery, or hysteroscopy are recommended for treating uterine niche in women with fertility requirements [18]. However, the risk of bladder injury and uterine perforation is higher in patients with a residual myometrium thickness of less than 3 mm [19].

At present, the mechanism of uterine niche is still unclear. Factors affecting cesarean section scar morphology during cesarean section include distance from the internal cervical os, uterine flexion, fetal birth weight and maternal age [20]. However, the healing of cesarean scar was not affected by the mode of caesarean section, type of uterine incision expansion and flexion, operator's experience, and stage of labor at the time of caesarean section [21]. Most women diagnosed with uterine niche are asymptomatic,



while some present with abnormal uterine bleeding [22]. Amanda et al. [3] suggested that major defects may be clinically related to abnormal uterine bleeding. Wang et al. [23] found that in patients diagnosed with uterine niche, the average defect width was significantly larger in patients with intermenstrual bleeding compared with patients without intermenstrual bleeding. This may be because a small niche is not enough to accumulate blood and may not show the symptoms of spotting [24], while a large niche will accumulate more blood, resulting in poor menstrual blood flow and intermenstrual bleeding [25]. However, the current study could not determine the threshold of niche size causing intermenstrual bleeding. In this study, there was no statistical difference in niche volume between OC and LNG-IUS groups.

For women with no fertility requirements and no contraindications, hormone therapy is reasonable for symptomatic treatment [8]. Two prospective studies showed an association between uterine niche and intermenstrual bleeding; therefore, intermenstrual bleeding was selected as the primary outcome indicator for treatment [26, 27]. The mechanism of hormonal treatment in managing abnormal uterine bleeding in uterine niche has not been clarified. Previous studies have found that estrogen-progesterone effectively treats chronic renal failure complicated by gastrointestinal capillary dilatation bleeding [28]. In contrast, another study found that estrogen-progesterone is effective in treating bleeding due to gastrointestinal vascular malformation [29], which may be due to hormonal alteration of coagulation status and improvement of endothelial cell integrity. Increased local vascularization of scar diverticula may be a cause of abnormal uterine bleeding, and Chen et al. [7] found increased local vascularization in 74.1% of patients with uterine niche via hysteroscopy. Thurmond [30] explored the efficacy of OC in four patients with uterine niche and spotting and found that spotting decreased in one patient and did not change in the other three. Tahara [31] investigated the effectiveness of OC in treating uterine niche with intermenstrual bleeding, and vaginal ultrasound revealed a significant reduction in local blood flow to the scarred diverticulum and improvement in intermenstrual bleeding in most cases after 3 to 6 months of treatment. Zhang et al. [11] also concluded that OC is effective in decreasing the duration of menstrual periods. This

study discovered that OC treatment was effective in more than 80% and 90% of patients after 3 and 6 months, respectively.

LNG-IUS is widely used for the treatment of heavy menstrual bleeding [32]. LNG-IUS can cause endometrial thinning and stromal atrophy, thereby reducing menstrual flow. Nearly 60% of the 31 patients with uterine niche treated with an LNG-IUS in this study had shortened menstrual cycles, and 13 patients showed symptoms of amenorrhea after 3 months of treatment. More than 30% of the patients in the LNG-IUS group had irregular vaginal spotting, a common side effect of an LNG-IUS. Therefore, it was impossible to distinguish whether uterine niche or LNG-IUS caused the bleeding. However, in the case of irregular spotting caused by either condition, patients felt that an LNG-IUS did not resolve their original symptoms and therefore considered it ineffective.

The common side effects in the OC group were nausea and breast tenderness; however, the symptoms were relatively mild, and the patients tolerated them and continued the treatment. Nausea symptoms gradually decreased with the duration of treatment. Low libido was also a common response in the OC group, which increased with follow-up time. Zethraeus [33] compared the effects of OC and the placebo group on sexual function and found that OC had no adverse effect on overall sexual function; however, desire, arousal, and pleasure were significantly lower in the OC group than in the placebo group. Therefore, low libido is a concern for patients treated with OC for a long time. The common side effects of an LNG-IUS include amenorrhea and irregular spotting. Irregular spotting may affect the judgment of the patient's menstrual period, and, thus, the judgment of the efficacy of an LNG-IUS. In addition, the LNG-IUS increased vaginal discharge, another adverse effect.

## **CONCLUSIONS**

In conclusion, this study demonstrated that OC was superior to an LNG-IUS in managing intermenstrual bleeding in uterine niche. The outcome may have been influenced by the side effects of spot bleeding associated with an LNG-IUS and needs to be confirmed by a larger sample and longer follow-up.

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### ***Conflict of interest***

All authors have no conflicts of interests to declare.

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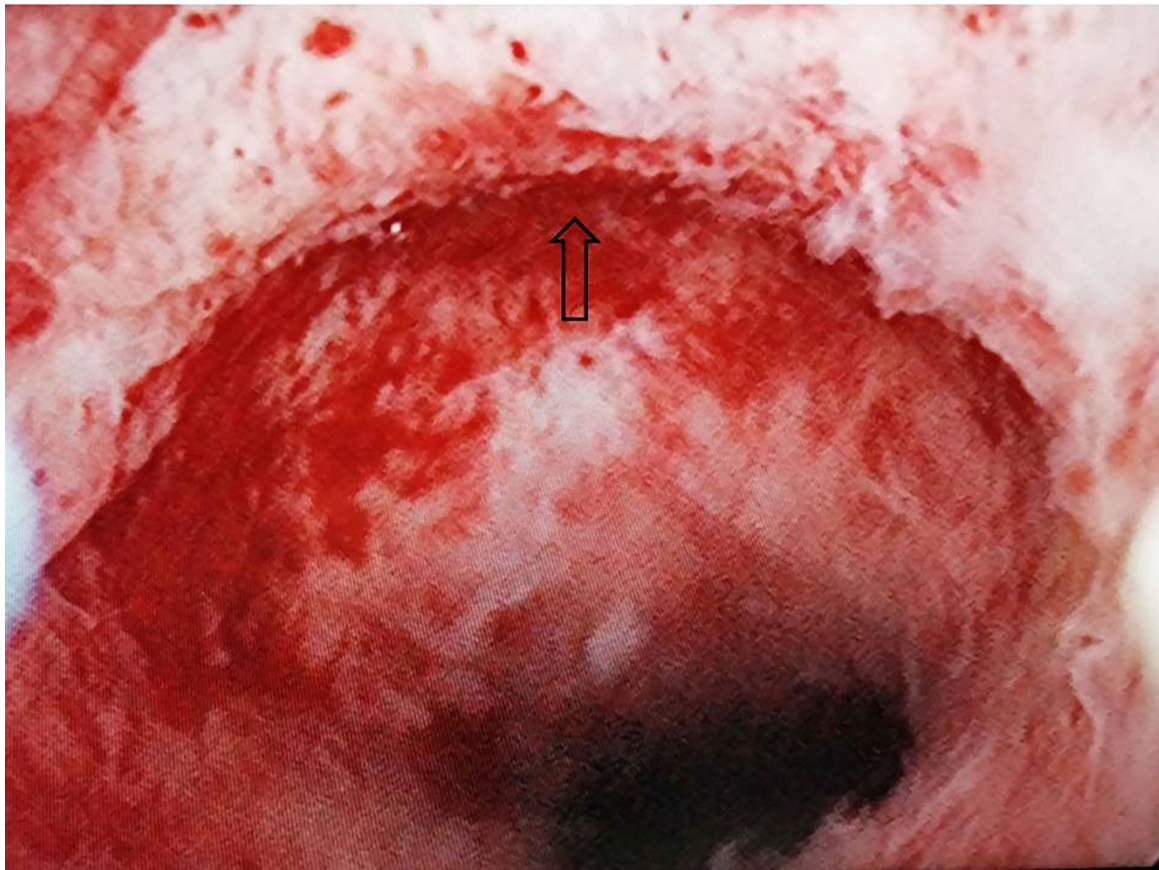
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**Figure 1.** Hysteroscopic view of a uterine niche from cervical canal. The arrow points to the roof of uterine niche.

**Table 1.** Baseline characteristics of patients in two groups

Characteristics	OC	LNG-IUS	p value
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	n = 41	n = 31	
Age (mean ± SD)	29.49 ± 2.50	30.61 ±	0.072
		2.69	
BMI (mean ± SD)	21.16 ± 1.64	21.45 ±	0.444
		1.47	
Gravidity [times] (mean ± SD)	2.73 ± 1.07	2.94 ± 1.50	0.504
Parity [times] (mean ± SD)	1.59 ± 0.63	1.68 ± 0.60	0.533
Previous abortions [times] (mean ± SD)	1.07 ± 0.91	1.16 ± 1.16	0.718
Number of CSs [times] (mean ± SD)	1.63 ± 0.66	1.74 ± 0.63	0.487
Interval between last CS and symptoms onset [months]			0.611
< 24	31 (75.61)	25 (80.65)	
> 24	10 (24.39)	6 (19.35)	
Niche volume [mm <sup>3</sup> ]			0.101
≤ 300	11 (26.83)	6 (19.35)	
300–600	9 (21.95)	2 (6.45)	
600–1200	13 (31.71)	10 (32.26)	
> 1200	8 (19.51)	13 (41.94)	
Residual myometrium thickness [mm]			0.475
≤ 3	19 (46.34)	17 (54.84)	
> 3	22 (53.66)	14 (45.16)	
Cycle length [days]			0.704
≤ 24	2 (4.88)	1 (3.23)	
25–29	16 (39.02)	13 (41.94)	
30–34	17 (41.46)	15 (48.39)	
≥ 35	6 (14.63)	2 (6.45)	
Length of menstruation, days (mean ± SD)	12.29 ± 2.99	11.65 ±	0.361
		2.92	
Uterine position			0.658
Anteflexed	23 (56.10)	19 (61.29)	
Retroflexed	18 (43.90)	12 (38.71)	

SD — standard deviation; BMI — body mass index; CS — cesarean section; OC — oral contraceptives; LNG-IUS — levonorgestrel intrauterine system

**Table 2.** Effectiveness of treatment in two groups

Follow-up time [months]	OC			LNG-IUS		
	1	3	6	1	3	6
valid	33 (80.49)	34 (82.93)**	38 (92.68)**	18 (58.06)	17 (54.84)	19 (61.29)



Shortend to ≤ 7 days	20 (48.78)	22 (53.66)	28 (73.08)	14 (45.16)	15 (48.39)	19 (61.29)
Still >7 days but shortend ≥ 3 days	13 (31.71)	12 (29.27)	10 (19.23)	4 (12.90)	2 (6.45)	0 (0.00)
invalid	8 (19.51)	7 (17.07)	3 (7.32)	13 (41.94)	14 (45.16)	12 (38.71)
No significant change or shortend < 3 days	8 (19.51)	7 (17.07)	3 (7.32)	13 (41.94)	14 (45.16)	12 (38.71)

OC — oral contraceptives; LNG-IUS — levonorgestrel intrauterine system; The use of OC was more effective than LNG-IUS in treating intermenstrual bleeding caused by uterine niche; \*p < 0.05; \*\*p < 0.01

**Table 3.** Adverse effects after treatment in two groups

Follow-up time [months]	OC			LNG-IUS		
	1	3	6	1	3	6
Nausea	6 (14.63)	2 (9.76)	1 (2.44)	0 (0.00)	0 (0.00)	0 (0.00)
Amenorrhea	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	13 (41.94)	14 (45.16)
Breast tenderness	5 (12.20)	6 (14.63)	6 (14.63)	0 (0.00)	0 (0.00)	0 (0.00)
Increased vaginal discharge	0 (0.00)	0 (0.00)	0 (0.00)	4 (12.90)	2 (6.45)	2 (6.45)
Irregular vaginal bleeding	0 (0.00)	0 (0.00)	0 (0.00)	6 (19.35)	10 (32.26)	12 (38.71)
Decreased libido	0 (0.00)	6 (14.63)	7 (17.07)	0 (0.00)	0 (0.00)	0 (0.00)

OC — oral contraceptives; LNG-IUS — levonorgestrel intrauterine system