

Effect of hysteroscopic cold-knife resection combined with dydrogesterone therapy on natural conception outcomes in women with endometrial polyps

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KEY WORDS

curettage,
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ABSTRACT

INTRODUCTION This study was conducted to explore the impact of hysteroscopic cold-knife resection (HCKR) combined with dydrogesterone on natural conception in patients with endometrial polyps (EPs). **AIM** We aimed to assess the clinical efficacy of HCKR combined with dydrogesterone in patients with EPs, focusing particularly on reproductive outcomes and natural conception rates.

MATERIALS AND METHODS A total of 110 patients with EPs were categorized into 2 groups: the cold-knife group, which underwent HCKR with dydrogesterone, and the control group, which received curettage with dydrogesterone. The comparisons included baseline data, surgical indicators (operative time, intraoperative bleeding, and length of hospital stay), postoperative complications, menstrual blood loss score (as per the Pictorial Blood Assessment Chart [PBAC]), endometrial thickness, postoperative fertility outcomes, including time to ovulation recovery and 12-month natural pregnancy rate, female sexual function (as measure via the Female Sexual Function Index [FSFI]) scores (desire, arousal, lubrication, orgasm, satisfaction, and pain), and sex hormone levels pre- and 1 month post-treatment.

RESULTS Both groups had similar baseline characteristics. The cold-knife group demonstrated shorter operative time, reduced intraoperative blood loss, shorter hospital stay, lower postoperative complication rates, reduced PBAC scores, thinner endometrial thickness, and better fertility outcomes. Both groups showed improved FSFI scores and decreased levels of estradiol, follicle-stimulating hormone, and luteinizing hormone post-treatment, with no significant intergroup differences in hormonal parameters.

CONCLUSIONS Hysteroscopic cold-knife resection combined with dydrogesterone is effective for treating EPs, improving surgical safety, recovery, and fertility outcomes.

INTRODUCTION Endometrial polyps (EPs) represent a prevalent gynecological pathology, with an estimated incidence of approximately 25% in women of reproductive and perimenopausal age.¹ Their formation is strongly influenced by several risk factors, including advancing age, estrogen dominance, hypertension, and long-term tamoxifen therapy. Histologically, EPs are characterized by localized hyperplastic growths of the endometrial glands and stroma, supported by a fibrovascular core.² They vary considerably in morphology and size—from a few millimeters to

several centimeters—and may occur as solitary or multiple lesions, most frequently in women aged 40–49 years.³ Although many EPs remain benign and asymptomatic, they can lead to a range of gynecological problems, such as abnormal uterine bleeding, infertility, and pelvic discomfort.⁴ Diagnostic confirmation typically relies on imaging or direct endoscopic visualization. Transvaginal ultrasonography serves as the first-line modality; however, its findings, such as hyperechoic intrauterine nodules or irregular endometrial contours, lack specificity.⁵ Evidence on

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the reproductive implications of EP management remains inconsistent. Current studies are insufficient to determine whether surgical excision of EPs translates into improved fertility outcomes, emphasizing the need for additional research exploring how restoration of endometrial architecture may enhance uterine receptivity before conception or assisted reproduction.⁶

Surgical removal remains the gold standard treatment for symptomatic or fertility-related EPs.⁷ Among available options, hysteroscopic polypectomy—including cold-knife resection, resectoscopy (bipolar or monopolar), and mechanical tissue removal systems, such as the Integrated Bigatti Shaver device (KARL STORZ SE & Co. KG, Tuttlingen, Germany)—provides direct visualization, precise excision, and minimal invasiveness.⁸⁻¹⁰ Polypectomy can be safely and effectively performed using rigid or semirigid hysteroscopes equipped with operative channels that accommodate cold instruments or miniaturized radiofrequency devices, enabling the procedure to be conducted in both inpatient and outpatient settings.¹¹ This approach offers high complete resection rates, low complication risks, and favorable fertility outcomes.¹² The hysteroscopic cold-knife resection (HCKR) technique involves mechanical dissection and retrieval of intrauterine lesions using micro-scissors and forceps under endoscopic guidance.¹⁰ Despite its advantages, recurrence after hysteroscopic removal remains variably reported.⁴ In contrast, blind curettage carries notable risks, including incomplete removal, hemorrhage, and secondary surgical intervention.¹³ Adjunctive hormonal therapy has been investigated to regulate endometrial proliferation and prevent recurrence. Dydrogesterone, a highly selective oral progestogen structurally similar to endogenous progesterone, exhibits excellent bioavailability, safety, and endometrial specificity.^{14,15} For luteal support, oral dydrogesterone can serve as an effective alternative or adjunct to vaginal progesterone, improving outcomes in some patients with insufficient serum progesterone.¹⁶

However, few studies have specifically examined the combination of HCKR with dydrogesterone, and evidence regarding their synergistic effect on postoperative fertility restoration remains limited. Moreover, whether hormonal modulation after complete EP excision can enhance spontaneous conception and long-term reproductive outcomes has not yet been systematically evaluated.

AIM We aimed to assess the clinical efficacy of HCKR combined with dydrogesterone in patients with EPs, focusing particularly on reproductive outcomes and natural conception rates.

MATERIALS AND METHODS Ethics This research was approved by the hospital's Ethics Committee of the Anting Hospital of Jiading District (2022071). All participants involved in the study signed written informed consent forms.

General study characteristics In total, 110 patients with EPs admitted from February 2022 to February 2024 were included in the analysis. Inclusion criteria encompassed: 1) a diagnosis of EPs confirmed on ultrasound or hysteroscopy; 2) fertility needs and a normal sexual life history; and 3) a history of irregular vaginal bleeding. Exclusion criteria comprised: 1) surgical contraindications; 2) coagulation disorders or hematological diseases; 3) other gynecological diseases or congenital reproductive organ malformations; and 4) infertility caused by immune, male-related, or other endocrine factors. The patients were assigned to either the cold-knife group or the control group based on the treatment received, with 55 participants in each cohort. The cold-knife group was treated with HCKR combined with dydrogesterone, and the control group received curettage and dydrogesterone. Baseline characteristics were similar between the groups, confirming the comparability of subsequent results. According to prior findings¹⁰ and data derived from a pilot experiment, mean (SD) Pictorial Blood Assessment Chart (PBAC) score 3 months following treatment for EPs was 129.2 (19.09) in the cold-knife group and 158.73 (20.57) in the control group. A 2-sided significance threshold of $\alpha = 0.05$ and a statistical power of 0.8 ($1-\beta$) were adopted for the analysis. When comparing the means of 2 independent samples, the parameters were substituted by the following formula

$$n = \frac{2(\sigma_1^2 + \sigma_2^2)(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2}{(\mu_1 - \mu_2)^2}$$

to calculate the sample size, with

$$n = \frac{2(19.65^2 + 16.24^2)(1.96 + 0.84)^2}{(136.78 - 186.82)^2} \approx 15$$

participants in each group ($n = 55$).

MATERIALS AND METHODS Both groups underwent surgery within 3–7 days after the end of menstruation, following standard preoperative examinations. Misoprostol tablets were administered 30 minutes before surgery to soften the cervix, and all procedures were performed under intravenous anesthesia.

In the cold-knife group, the procedure was performed under direct hysteroscopic visualization using the cold-knife technique. At the beginning of the surgery, a 0.9% normal saline solution was continuously infused into the uterine cavity via a distension pump, separating the anterior and posterior uterine walls, and providing a clear, stable operative field. Through the video imaging system, the surgeon could observe the uterine cavity in real time, accurately identifying the base and margins of the polyp. The cold-knife instrument was introduced through the hysteroscope's working channel, and, under direct visualization, the blade was positioned at the lower margin of the polyp stalk to mechanically excise the tissue

in sections, ensuring complete removal while preserving uterine and reproductive integrity.

In the control group, conventional curettage was performed. Prior to the operation, the location and number of EPs were identified on ultrasound and hysteroscopy. Under strict aseptic conditions, the cervix was gradually dilated using cervical dilators until a No. 6 dilator could pass smoothly. Based on the estimated size and morphology of the polyps, an appropriately sized curette was selected and inserted into the uterine cavity. Guided by tactile feedback and preoperative imaging, systematic and comprehensive scraping was conducted along the uterine wall where the polyps were located, detaching the lesions from their base. The detached tissue fragments were then aspirated using a negative-pressure suction device and sent for histopathologic examination to confirm the diagnosis.

Following surgery, all patients were prescribed dydrogesterone tablets, starting from day 5 of the menstrual cycle. The dosage was 10 mg twice daily for 21 consecutive days per cycle, continued for 3–6 menstrual cycles based on a physician's recommendation.

All patients were followed up through outpatient visits and telephone calls for 12 months to monitor postoperative recovery and reproductive outcomes.

Evaluation criteria The operative time, intraoperative blood loss, and length of hospital stay were recorded for both groups. Within 3 months postoperatively, the occurrence of complications, such as irregular uterine bleeding, secondary infection, menstrual disorders, and urinary retention, was monitored and documented.

The PBAC score¹⁷ and endometrial thickness pretreatment and 3 months post-treatment were recorded. The PBAC is a standardized quantitative instrument applied to assess the severity of postpartum bleeding, with a validity coefficient of 0.851. It comprises 3 domains: physiological status, resuscitative interventions, and etiological factors of hemorrhage. The minimum score is 0, and there is no upper limit; a higher score reflects greater blood loss and more severe clinical condition. Endometrial thickness was measured on transvaginal ultrasonography. During the procedure, the patients were required to empty their bladder, and the transducer was inserted into the vagina to assess the double-layer thickness of the endometrium in the sagittal plane.

The time to ovulation recovery and natural conception rate within 12 months postoperatively were recorded for both groups. Ovulation recovery was evaluated using ovulation test strips (luteinizing hormone [LH] test papers; Lepzi, Sofia, Bulgaria). Urine samples were tested daily at the same time to estimate the LH surge. When the color intensity of the test line was equal to or darker than that of the control line, the result was deemed positive, indicating imminent ovulation. The day with a distinct LH surge was recorded

as the day ovulation signal occurred. Successful natural conception within 12 months postsurgery was determined during follow-up and confirmed when serum β human chorionic gonadotropin levels exceeded the reference threshold (>5 – 10 mIU/ml).

The Female Sexual Function Index (FSFI) score¹⁸ was recorded prior to and 3 months following treatment. The FSFI is a validated instrument with a reliability coefficient of 0.802, comprising 6 domains: sexual desire, arousal, vaginal lubrication, orgasm, satisfaction, and dyspareunia. Each domain is scored up to 6 points, with a total score of 36. Higher scores indicate better sexual function and overall sexual quality of life.

Serum sex hormone levels, including estradiol (E_2), follicle-stimulating hormone (FSH), and LH, were measured before and 1 month after treatment. For the analysis, 5 ml of peripheral venous blood was collected from each patient. The samples were centrifuged for 15 minutes at 3000 revolutions/min, and the supernatant was separated post-standing. Hormone concentrations were examined using chemiluminescence immunoassay. For E_2 detection, the serum samples were incubated with a defined amount of luminescently labeled E_2 analog (Ortho Clinical Diagnostics, Raritan, New Jersey, United States). The intensity of emitted light is inversely proportional to serum E_2 concentration—the higher the E_2 level, the fewer labeled molecules bind to antibodies, producing weaker luminescence. For FSH and LH assays, monoclonal antibodies specific to FSH (Snibe Diagnostics, Shenzhen, China) and LH (Bioscience, Shanghai, China) were employed. Both hormones in the sample simultaneously bound to solid-phase antibodies and labeled antibodies, forming a “sandwich” complex of solid-phase antibody–antigen–labeled antibody. The light signal intensity was directly proportional to the serum concentration of FSH or LH, providing a quantitative measurement of hormonal levels.

Statistical analysis All statistical procedures were implemented with SPSS Statistics software, version 25.2 (IBM Corp., Armonk, New York, United States) and GraphPad Prism, version 10.0 (Dotmatics, Boston, Massachusetts, United States). Prior to the analysis, the Kolmogorov–Smirnov test was applied to evaluate data normality. Variables exhibiting an approximately normal distribution were summarized as mean (SD). For comparisons, the paired *t* test was utilized for within-group data, and the independent-samples *t* test for between-group data. Non-normally distributed variables were expressed as median (interquartile range [IQR]), and their differences were examined with the Wilcoxon signed-rank test (paired samples) or the Mann–Whitney test (independent samples). Categorical variables were described as frequencies or percentages, and intergroup differences were evaluated using the χ^2 test. All

TABLE 1 General characteristics of the groups

Variable	Cold-knife group (n = 55)	Control group (n = 55)	t value	P value
Age, y	32.24 (3.27)	31.45 (2.96)	1.315	0.19
Polyp diameter, cm	2.59 (0.43)	2.47 (0.54)	1.289	0.02
Disease duration, mo	14.73 (3.03)	14.87 (2.99)	0.253	0.8
Number of polyps	Single	21 (38.18)	0.039	0.84
	Multiple	34 (61.82)		

Data are presented as mean (SD) or number (percentage).

TABLE 2 Operative time, intraoperative blood loss, and length of hospital stay

Variable	Cold-knife group (n = 55)	Control group (n = 55)	t/z value	P value
Operative time, min	22.76 (2)	26.05 (2.21)	8.18	<0.001
Intraoperative blood loss, ml	22.45 (3.89)	26.04 (4.41)	4.519	<0.001
Length of hospital stay, d	5 (5–5.5)	4 (4–5)	5.137	<0.001

Data are presented as mean (SD) or median (interquartile range).

TABLE 3 Types and incidence of postoperative complications

Variable	Cold-knife group (n = 55)	Control group (n = 55)	χ^2 value	P value	
Complication	Irregular uterine bleeding	1 (1.82)	3 (5.45)	–	–
	Secondary infection	0	2 (3.64)	–	–
	Menstrual disorders	0	2 (3.64)	–	–
	Urinary retention	0	1 (1.82)	–	–
Incidence rate	1 (1.82)	8 (14.55)	5.93	0.02	

Data are presented as number (percentage).

TABLE 4 Pictorial Blood Assessment Chart score and endometrial thickness

Variable		Cold-knife group (n = 55)	Control group (n = 55)	t value	P value
PBAC score, points	Pretreatment	314.49 (22.02)	312.45 (18.45)	0.526	0.6
	Post-treatment	129.2 (19.09) ^a	158.73 (20.57) ^a	7.804	<0.001
Endometrial thickness, mm	Pretreatment	12.95 (1.57)	13.38 (1.78)	1.348	0.18
	Post-treatment	5.44 (1.22) ^a	6.65 (1.51) ^a	4.652	<0.001

Data are presented as mean (SD).

^a As compared with the same group before treatment, $P < 0.05$

Abbreviations: PBAC, Pictorial Blood Assessment Chart

tests were 2-tailed, and a P value below 0.05 denoted significance.

RESULTS General information Baseline characteristics, such as, polyp diameter, disease duration,

and polyp number, were comparable between the groups (TABLE 1).

Operative metrics In comparison with the controls, the cold-knife cohort experienced shorter operative time, reduced intraoperative bleeding, and briefer hospitalization ($t/z = 8.18; 4.519; 6.513$, respectively; $P < 0.001$; TABLE 2).

Postoperative complications Postoperative complications occurred in 1.82% of the patients in the cold-knife group ($n = 1$) and 14.55% of the controls ($n = 8$), yielding a lower incidence with cold-knife management ($\chi^2 = 5.93; P = 0.02$; TABLE 3).

Pictorial Blood Assessment Chart score and endometrial thickness At baseline, PBAC scores and endometrial thickness were comparable. Three months postsurgery, both indices declined notably from the pretreatment levels in both groups, with greater reductions in the cold-knife cohort ($t = 7.804; 4.652$, respectively; $P < 0.001$; TABLE 4).

Fertility outcomes Relative to the controls, the cold-knife group demonstrated a faster return to ovulation ($z = 8.498; P < 0.05$) and a higher spontaneous pregnancy rate within 12 months postsurgery ($t = 5.546; P = 0.02$; TABLE 5).

Sexual life quality Before treatment, the FSFI scores did not differ between the groups. Following treatment, both cohorts improved their desire, arousal, lubrication, orgasm, satisfaction, and pain scores, with no between-group differences (TABLE 6).

Sex hormone profiles Baseline E₂, FSH, and LH levels were similar. One month post-treatment, all 3 hormones decreased noticeably relative to the baseline values in both groups without intergroup differences (TABLE 7).

DISCUSSION The pathogenesis of EPs remains incompletely understood, and no definitive cure currently exists. EPs are frequently detected in premenopausal women with reproductive difficulties.^{19,20} In women of reproductive age, EPs are a recognized contributor to infertility—by distorting the uterine cavity and disrupting local endometrial architecture, they hinder embryo implantation and may precipitate early pregnancy loss.⁹ Medical management—cyclic progestins or levonorgestrel-releasing intrauterine systems—represents a nonsurgical alternative in selected cases.²¹ Against this background, our study compared HCKR combined with dydrogesterone with curettage and dydrogesterone, focusing on natural conception. Across the outcomes, the HCKR-based protocol consistently outperformed the comparator.

Perioperative performance favored HCKR. The cold-knife group had notably shorter operative times, less intraoperative bleeding, and shorter hospitalization. Unlike blind curettage,

TABLE 5 Postoperative fertility indicators of the groups

Variable	Cold-knife group (n = 55)	Control group (n = 55)	z/χ^2 value	<i>P</i> value
Time to recovery of ovulation after surgery, d	2 (2–3)	4 (3–4)	8.498	<0.001
Spontaneous pregnancy rate within 12 months of surgery	27 (49.09)	15 (27.27)	5.55	0.02

Data are presented as number (percentage) or median (interquartile range).

TABLE 6 Sexual life quality of the groups as per the Female Sexual Function Index (points)

Variable		Cold-knife group (n = 55)	Control group (n = 55)	<i>z</i> value	<i>P</i> value
Sexual desire	Pretreatment	3 (3–3)	3 (3–3)	0.786	0.43
	Post-treatment	4 (3–5) ^a	4 (3–5) ^a	0.758	0.45
Arousal	Pretreatment	3 (3–3)	3 (3–3)	1.29	0.2
	Post-treatment	4 (4–5) ^a	4 (3–5) ^a	1.198	0.23
Vaginal lubrication	Pretreatment	3 (3–3)	3 (3–3)	0.86	0.39
	Post-treatment	4 (3–5) ^a	4 (3–5) ^a	0.738	0.46
Orgasm	Pretreatment	3 (3–3)	3 (3–3)	0.959	0.34
	Post-treatment	4 (3–5) ^a	4 (3–5) ^a	0.75	0.45
Sexual satisfaction	Pretreatment	3 (3–3)	3 (3–3)	0.859	0.39
	Post-treatment	4 (3–5) ^a	4 (3–5) ^a	0.022	0.98
Dyspareunia	Pretreatment	3 (3–3)	3 (3–3)	0.852	0.39
	Post-treatment	4 (3–5) ^a	4 (3–5) ^a	1.101	0.27

Data are presented as median (interquartile range).

a As compared with the same group before treatment, $P < 0.05$

TABLE 7 Sex hormone levels before and after treatment in the study population

Hormone		Cold-knife group (n = 55)	Control group (n = 55)	<i>t</i> value	<i>P</i> value
E_2 , pmol/l	Pretreatment	453.24 (19.21)	453.34 (22.08)	0.024	0.98
	Post-treatment	157.16 (14.45) ^a	159.07 (13.87) ^a	0.706	0.48
FSH, IU/l	Pretreatment	7.14 (0.9)	7.34 (1.01)	1.102	0.27
	Post-treatment	4.37 (0.99) ^a	4.20 (0.86) ^a	0.98	0.33
LH, IU/l	Pretreatment	6.27 (1.2)	6.20 (1.08)	0.32	0.75
	Post-treatment	4.58 (1.12) ^a	4.45 (1.41) ^a	0.545	0.59

Data are presented as mean (SD).

a As compared with the same group before treatment, $P < 0.05$

Abbreviations: E_2 , estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone

which depends on tactile feedback and recall of preoperative imaging, HCKR employs continuous endoscopic visualization, providing a magnified, nonblind view of the cavity. This allows for a precise identification of the polyp pedicle and stepwise mechanical excision under direct vision, limiting collateral damage to the adjacent endometrium, curtailing bleeding by avoiding broad, vascular scraping, and preventing time-consuming trial-and-error maneuvers. In parallel, mechanical hysteroscopic tissue-removal systems can streamline procedures by minimizing device

exchanges and reducing distension media exposure.²² Postoperative complications were also less frequent with HCKR, likely reflecting the technique's tissue-sparing nature and preservation of the endometrial basal layer. In contrast, curettage carries a risk of scarring and intrauterine adhesions.²³ Importantly, targeted pedicle resection with HCKR enhances the probability of complete polypectomy.

Endometrial milieu and fertility outcomes further support the superiority of HCKR over blind curettage. After treatment, the cold-knife cohort exhibited lower PBAC scores and a thinner endometrium, alongside better reproductive indicators. These findings are consistent with the notion that cold-knife techniques optimize the uterine environment for implantation. Experience from hysteroscopic myomectomy indicates that cold-knife mechanical dissection affords a clean tissue plane and maximal endometrial preservation, as compared with electrosurgical approaches, with minimal disruption of the subjacent myometrium.²⁴ By avoiding thermal injury, HCKR helps maintain the integrity of the endometrial base and the ovarian blood supply. This tissue protection aligns with our observation of quicker ovulation resumption in the cold-knife group, enabling earlier entry into the fertile window. Li et al²⁴ similarly highlighted potential advantages of cold-knife methods in hysteroscopic surgery and assisted reproduction among women seeking fertility.

In terms of sexual function, both groups experienced significant post-treatment gains across the FSFI domains, with no between-group differences, which echoes previous reports.^{25,26} This pattern suggests that the improvement in sexual quality of life is primarily attributable to dydrogesterone, rather than the surgical modality itself. Dydrogesterone is widely used for menstrual disturbances and endocrine imbalance, and is also employed in miscarriage prevention.¹⁴ Sexual desire is critically shaped by nuanced neuroendocrine dynamics.²⁷ Consistent with this, hormone profiling showed significant post-treatment reductions in estradiol, FSH, and LH levels in both groups, without intergroup disparities. Notably, dydrogesterone has demonstrated efficacy comparable to that of antagonist protocols in preventing premature LH surge,²⁸ which may partly explain the similar hormonal trajectories observed in our analysis.

Our study has certain limitations to be acknowledged. A 1-year horizon is sufficient for short-term fertility assessment but may not capture long-term end points, including EP recurrence or outcomes of subsequent pregnancies (eg, miscarriage risk). Moreover, we did not stratify by critical modifiers, such as polyp size, their number, or patient age, which could influence response to therapy. Future studies should incorporate longer follow-up, recurrence surveillance, and stratified analyses to refine patient selection and optimize individualized treatment pathways.

CONCLUSIONS In women with EPs, HCKR combined with dydrogesterone outperformed curettage and dydrogesterone regimen in perioperative metrics, complication rates, endometrial bleeding burden and thickness, and fertility outcomes within 12 months. FSFI and hormone profiles improved in both study arms, without between-group differences. Clinically, HCKR with dydrogesterone is a reasonable first-line choice when fertility preservation is prioritized; however, confirmation of durability and recurrence risk requires longer observation.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

AI STATEMENT Artificial intelligence was not used in the preparation of this manuscript.

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