ORIGINAL ARTICLE: GYNECOLOGY AND MENOPAUSE

High number of endometrial polyps is a strong predictor of recurrence: findings of a prospective cohort study in reproductive-age women

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Objective: To compare the incidence of recurrence between a cohort with a high number (≥ 6) of endometrial polyps (EPs) and a single-EP cohort among reproductive-age patients after polypectomy.
Design: Prospective observational cohort study.
Setting: Single university center.
Patient(s): Premenopausal women who underwent hysteroscopic endometrial polypectomy were recruited.
Intervention(s): Patients underwent a transvaginal ultrasound scan every 3 months after polypectomy to detect EP recurrence. Kaplan-Meier and Cox regression models were used to compare the risk of recurrence between the two cohorts and analyze the potential risk factors for EP recurrence.
Main Outcome Measure(s): EP recurrence rate.
Result(s): The study enrolled 101 cases with a high number of EP and 81 cases with a single EP. All baseline parameters were similar except that the high number of EP cohort had a slightly lower mean age than the single EP cohort (33.5 [range 30.0–39.0] vs. 36.0 [30.5–43.0] years). The risk of recurrence in the high number of EP cohort was 4.08 (95% confidence interval [CI] 1.89–8.81) times higher than that in the single-EP cohort 1 year after polypectomy, with a recurrence rate of 45.5% versus 13.4%, respectively. A high number of EPs, endometriosis, and previous polypectomy history were independently associated with polyp recurrence.
Conclusion(s): The high number of EP cohort was much more prone to recurrence than the single-EP cohort. A high number of EPs, endometriosis, and previous polypectomy history were independent risk factors for recurrence. A high number of EPs is suggested to be a distinct subgroup with different pathogenesis, which warrants frequent monitoring and prevention. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Hysteroscopy, polypectomy, endometrial polyps, recurrence

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Endometrial polyp (EP), a common gynecologic condition for which abnormal uterine bleeding (AUB) is the most common presenting symptom, is defined as localized overgrowth of the endometrial glands and stroma around a vascular core that projects from the surface of the endometrium (1). Its prevalence ranges from 7.8% to 34.9% in routine clinical practice and is higher in infertile women (2).

Intrauterine structural abnormalities are thought to perturb implantation and cause infertility as well as early pregnancy loss (3, 4), and the presence of EPs is suggested to be the most common pathologic finding detected by office hysteroscopy in subjects with recurrent implantation failure (5). The molecular mechanisms of polyps

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causing infertility are mainly related to defective endometrial receptivity. EPs can induce local inflammatory changes (6, 7), produce glycodelin to inhibit natural killer cell activity, and decrease the expression of essential receptivity molecular markers, such as HOXA10 and HOXA11 (8). Other studies propose that EPs may present an abnormal site that interferes with sperm transportation as well as embryo implantation (9).

In addition to scientific evidence, polypectomy has been proven to increase pregnancy rates of spontaneous conception as well as assisted reproduction in infertile patients (10, 11). As such, clinical practice guidelines recommend mandatory surgical EP removal in women seeking pregnancy because of its negative effect on embryo implantation and the demonstrated benefits of surgical removal (3, 12).

Hysteroscopic polypectomy, now the criterion standard for the diagnosis and treatment of EP, is performed under direct visualization to completely remove EPs but leave the adjacent endometrium intact (13). However, although hysteroscopic resection effectively removes polyps, EP recurrence remains a concern with recurrence rates of 2.5%–43.6% (13–16). As such, it is critical to identify the risk factors for EP recurrence, especially in reproductive-age women desiring future conception, to aid in clinical counseling and decision making.

Limited data are available in the literature that explore risk factors for EP recurrence, in part owing to the time-consuming nature of a prospective cohort study. Only a few retrospective studies to date have explored EP recurrence risk factors, and they have reported conflicting results and mostly focused on postmenopausal women (13, 15, 16). Although some studies have suggested that EP number did not correlate with recurrence potential, those studies included subjects with only 2–3 polyps in multiple-EP cohorts; cases with >5 polyps have never been discussed (13, 17). In contrast, Yang et al. (14) focused a retrospective study for the first time on the EP recurrence potential of reproductive-age women and suggested that a high number of EPs was a strong predictor for recurrence. Yang et al.'s findings suggested that a subgroup with ≥6 polyps could reach a recurrence rate as high as 59% after an average of 18 months of follow-up, which was much higher than those with a single EP or 2–3 EPs with recurrence rates of 35% and 36%, respectively (14). However, the validity of Yang et al.'s study result may have been compromised by the retrospective study design with different follow-up time points. Accordingly, we designed a 1-year prospective cohort study to compare the recurrence rates with a high number of EPs or a single EP and to explore the potential risk factors for EP recurrence among reproductive-age women.

MATERIALS AND METHODS

Study Design and Patient Selection

This single-center prospective cohort study enrolled premenopausal women who had EPs and underwent hysteroscopic polypectomy in the First Affiliated Hospital of Sun Yat-sen University from January 5, 2015, to January 4, 2016. These women were awaiting a future pregnancy, although some did not plan to conceive immediately. The study included two cohorts of subjects, the single-EP cohort and the high number of EP cohort, for comparison of the relative risk of EP recurrence. The study was reviewed and approved by the Institutional Committee of Ethics for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University, People's Republic of China. There were no conflicts of interest associated with this study.

Inclusion criteria were premenopausal status with a diagnosis of benign EP confirmed by means of hysteroscopy and histopathology with full EP removal. The histology of the EP was confirmed based on the criterion of irregular endometrial glands with thick-walled vessels scattering in fibrous or collagenous stroma (18). The present study intentionally recruited two divergent cohorts of patients with a single versus ≥6 EPs based on the EP number found during the hysteroscopy examination. The rationale for having single versus ≥6 EPs cohorts was based on quartile cutoff point from our pilot study. We observed that the EP number quartile cutoff points among premenopausal EP patients who underwent polypectomy in our hospital were: 1st quartile = 1; 2nd quartile = 2–3; 3rd quartile = 4–5; and 4th quartile ≥6. Therefore, we decided to recruit patients with the lowest quartile of EP numbers (single EP) and the highest quartile of EP numbers (≥6 EPs) as the single-EP cohort versus the high number of EP cohort. Women who received hormone contraception, hormone replacement therapy, controlled ovarian stimulation, and medications that affect the endometrium, such as tamoxifen after surgery, were excluded from the study. Women with atypical or hyperplastic EPs were also excluded.

Office Hysteroscopy

Office hysteroscopy was scheduled in the follicular phase after menstruation (days 5–12 of the cycle) for EP diagnosis and localization. It was performed with the use of a hysterovideoscope (Hopkins II 30°; Storz) with an outer diameter of 5 mm. After speculum application and cervical disinfection, the hysteroscope was introduced intracervically. The uterine cavity was distended with the use of 0.9% sodium chloride solution. The fluid was introduced by means of an automated hysteroscopic distension pump at an inflow pressure of 100–110 mm Hg. The hysteroscopic polypectomy was performed with the use of a small ovum forcep for blunt removal with the help of hysteroscopy for targeting the EPs. The remaining small pedicle was curetted if necessary. Hysteroscopy was used to reinspect the uterine cavity to confirm complete EP removal. The specimen was then sent for histopathology analysis. We avoided using diathermy to prevent deep injury to the endometrium, which might be unfavorable for embryo implantation. All of these procedures were performed exclusively by the same experienced physician (H.Z.).

Patient Enrollment and Data Collection

Subject recruitment occurred when patients returned to obtain their histologic and hysteroscopy reports 2 weeks after office hysteroscopy, and eligible patients were recruited based

on the aforementioned inclusion criteria. Written informed consent was obtained before data collection. Baseline data about their demographic, gynecologic, obstetrical, and medical histories; indications for surgery (infertility and/or AUB); numbers and diameters of EPs; and histopathologic features were collected. Infertility was defined as failure to conceive after 1 year of regular intercourse without contraception. AUB was defined as prolonged menstrual bleeding >7 days in duration or the presentation of any intermenstrual bleeding (2, 8).

Follow-up

The primary outcome measure was the recurrence rate of EP within 1 year after polypectomy, defined as the percentage of patients with EP recurrence at each follow-up time point as detected by means of transvaginal ultrasound with color Doppler (TVCD). Patients were scheduled for a follow-up with TVCD to screen for EP recurrence at 3, 6, 9, and 12 months after the initial full surgical EP removal. All scans were performed in a standardized manner by the same physician (S.R.), who was blinded to the subjects' group assignments. First, the cervix and uterine corpus were identified in the transverse plane. Second, the uterine corpus was assessed by examining a series of parallel scanning planes, from the internal cervical os to the uterine fundus, to detect uterine anomalies (19). The ultrasound features of benign EPs are focal hyperechoic lesions presenting smooth and well defined borders with single feeder vessels on Doppler examination (20). Patients with negative findings on TVCD were all defined as "nonrecurrence."

Sample Size Estimation

Based on Yang et al.'s study, which showed a 59% recurrence rate in the high number of EP group versus 35% in the single-EP group (14), we calculated that a sample of 67 subjects in each cohort would have 80% power to detect an estimated difference of 24% points in the EP recurrence rate between the high-number and single-EP cohorts by means of Pearson chi-square two-sided test with a type I error of 0.05. Anticipating a 20% attrition rate, the final sample was increased to 80 per cohort.

Statistical Analyses

All analyses were conducted with the use of SPSS version 23.0. Intergroup differences were compared with the use of the Mann-Whitney *U* test or Student *t* test for continuous variables depending on the distribution of the data. Categoric variables were analyzed with the use of the chi-square test. Data are expressed as median (interquartile range), mean ± SD, or percentage. The Kaplan-Meier method with the log-rank test was used to estimate recurrence-free survival and to compare recurrence rates between the two cohorts. Survival was calculated from the date of polypectomy to the date of recurrence. Subjects without recurrence were censored at the last ultrasound examination. Cox regression models were used to compare the risk of recurrence between the high number of EP cohort and the single-EP cohort in both univariate and multivariate analyses. Factors with values of $P<.02$ on univariate analyses were included in the subsequent multivariable model, and factors with values of $P<.05$ on multivariate analyses were considered to be statistically significant.

RESULTS

A total of 182 women were included in the study, with 101 subjects (55%) in the high number of EP cohort and 81 (44.5%) in the single-EP cohort. All subjects underwent the follow-up 3 months after the initial surgery except for two because of pregnancy; 170 subjects completed the 6-month follow up; 157 subjects came back for an ultrasound examination at 9 months, and 152 subjects remained for the 12-month final checkup. The total dropout rate for 1 year was 16.4% (Fig. 1).

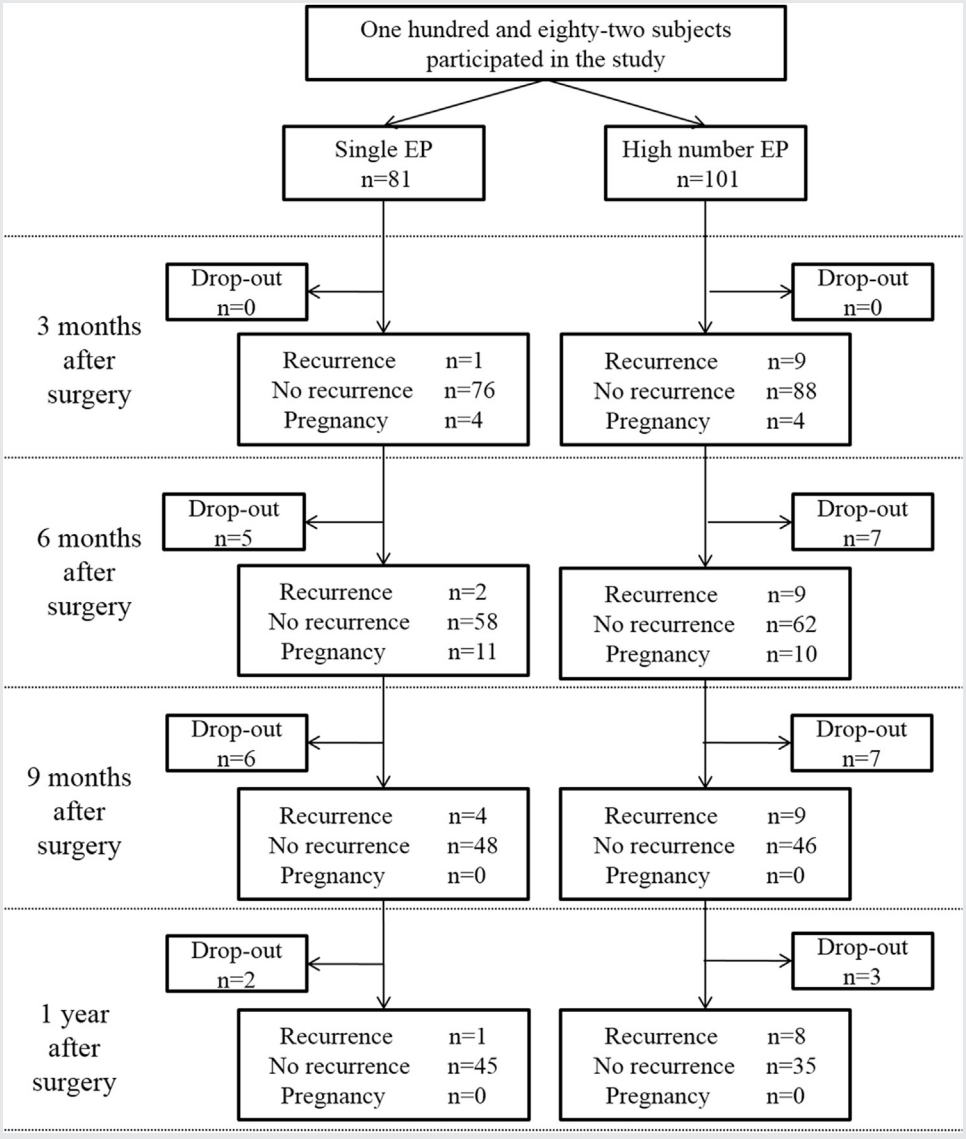
Demographics

Details of the study population are listed in Table 1. The subjects' median age in the high number of EP cohort was 33.5 years (30.0–39.0) versus 36.0 years (30.5–43.0) in the single-EP cohort ($P<.05$). Infertility and AUB were the two major indications for hysteroscopic polypectomy, and their proportions were similar between the two cohorts. The two cohorts did not differ significantly in body mass index (BMI), gravid and parity, history of polypectomy, and other possible risk factors for polyp recurrence, such as endometriosis, adenomyosis, polycystic ovary syndrome (PCOS), and leiomyoma. The mean polyp size was smaller in the high number of EP cohort than in the single-EP cohort (0.71 ± 0.30 cm vs. 0.94 ± 0.44 cm; $P<.05$).

A total of 43 subjects (32%) experienced EP recurrence in the entire cohort 1 year after polypectomy. The frequency of EP recurrence was much higher in the high number of EP cohort than in the single-EP cohort. After 1 year of follow-up, 45.5% (95% confidence interval [CI] 33.9%–57.0%) of subjects in the high number of EP cohort had EP recurrence, compared with only 13.4% (4.6%–22.2%) in the single-EP cohort. The hazard ratio (HR) for recurrence in the high number of EP cohort compared with the single-EP cohort was 4.08 (95% CI 1.89–8.81; $P<.01$). In addition, EP recurrence rates were significantly higher in patients with a high number of EPs than in those with a single EP at each monitoring time point, i.e., 8.9% versus 1.2% at 3 months, 20.0% versus 4.1% at 6 months, and 33.1% versus 11.5% at 9 months; $P<.05$ (Fig. 2).

Table 2 presents the univariate and multivariate Cox regression models that were used to evaluate the risk factors for EP recurrence. First, univariate analysis was used to determine the relationship between EP recurrence and its potential risk factors, including age, BMI, gravidity and parity, number of EPs, polyp size, previous history polypectomy, endometriosis, adenomyosis, PCOS, leiomyoma, and infertility. In the univariate analysis, a high number of EPs, infertility, endometriosis, adenomyosis, and previous polypectomy history were associated with the potential recurrence of EP ($P<.2$). Subsequent multivariate analysis showed that a high number of EPs (HR 3.45, 95% CI 1.41–8.47; $P<.01$), previous

FIGURE 1



Flow chart of the two cohorts over 1 year of follow-up after polypectomy. EP = endometrial polyp.

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polypectomy history (HR 2.42, 1.13–5.41; $P<.05$), and endometriosis (HR 2.18, 1.03–4.62; $P<.05$) were significant predictors of EP recurrence after adjusting for other factors.

DISCUSSION

To our knowledge, this is the first prospective cohort study to investigate the potential of postoperative polyp recurrence and its associated risk factors among premenopausal women. The findings indicated that subjects with excessive growth of multiple EPs (≥ 6) were much more vulnerable to recurrence than those with a single EP, even after adjustment for other potential risk factors (HR 3.45). Recurrence can occur very soon after surgery, and the incidences were much more frequent in the high number of EP cohort at each follow-up time point, i.e., at 3, 6, and 9 months after the initial surgery. In addition to the high EP numbers, this study also showed that previous histories of endometriosis and polypectomy were independent risk factors for EP recurrence, whereas other potential predictors, such as age, BMI, leiomyoma, infertility, and PCOS status, seemed not to have an effect.

The present study demonstrated that a high number of EPs increased the risk of recurrence in reproductive-age women, with an annual recurrence rate of 45.5% compared with 13.4% in the single-EP cohort. The study identified that patients with a high number of EPs growing excessively around the uterine cavity comprised a distinct high-risk subgroup that was previously neglected. The findings of this 1-year prospective cohort study confirmed the results of Yang et al.'s study, which first reported a significantly higher

TABLE 1

Comparison of patient demographics between groups.

Characteristic	High number of EPs (n = 101)	Single EP (n = 81)	*P* value
Age (y)	33.5 (30.0–39.0)	36.0 (30.5–43.0)	< .05
BMI (kg/m^2)	21.3 (19.6–22.6)	21.2 (19.5–23.7)	.60
AUB (%)	28.7 (29)	40.7 (33)	.13
Infertility (%)	57.4 (58)	49.3 (40)	.42
Multigravida (%)	51.5 (52)	48.1 (39)	.13
Previous polypectomy (%)	13.8 (14)	8.6 (7)	.31
Endometriosis (%)	13.9 (14)	24.6 (20)	.09
Adenomyosis (%)	4.0 (4)	11.0 (9)	.10
Leiomyoma (%)	12.8 (13)	16.0 (13)	.64
PCOS (%)	6.9 (7)	7.4 (6)	.73
Polyp size (cm)	0.71 ± 0.30	0.94 ± 0.44	< .01

Note: Values are presented as median (interquartile range), % (n), or mean ± SD. AUB = abnormal uterine bleeding; BMI = body mass index; EP = endometrial polyp; PCOS = polycystic ovary syndrome. A

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recurrence potential for subjects with a high number of EPs (≥6), showing a 59% recurrence rate after surgery versus a 35% recurrence rate in those with a single EP (14). However, Yang et al.'s study retrospectively investigated patients who presented to the same clinic a second time for a hysteroscopy examination, which was prone to selection and information bias, and showed a much higher EP recurrence rate than other studies. The annual recurrence rate of 13.4% in our single-EP cohort was in line with the results of previous studies (13, 21), but the annual recurrence rate of 45.5% in our high number of EP cohort was higher than those reported by most studies in the literature (13, 15, 17). The reasons for the relatively high recurrence rate may be due in part to the variety of study subjects as well as the different methods used for EP removal. Because our subjects were all reproductive-age women desiring a future pregnancy, all EPs were bluntly removed without the use of diathermy for fear of intrauterine adhesions, which have a potential unfavorable effect on future reproductive function (22). The blunt removal of polyps under outpatient hysteroscopy guidance is cost-effective for infertile women because it has been proven to not be inferior to other techniques in terms of clinical outcomes (23). In contrast, in other studies, EP resections were performed with the use of a resectoscope to fully remove the EP, including the stalks and base, at a depth of ≥5 mm up to the border of the myometrium (13, 15).

The correlation between EP number and recurrence potential has seldom been discussed and with contradictory results. Because there has been no specific definition of multiple/high-number EPs in the literature, we prospectively studied cohorts of patients in the highest quartile versus the lowest quartile of the polyp number from populations who underwent polypectomy in our hospital. Consistent with our patient grouping, Yang et al.'s retrospective (9) study also demonstrated that EP numbers ≥6 was associated with a much higher recurrence rate than a single EP, although EP numbers 2–3 shared a recurrence rate similar to that of a single EP. Regarding these results, we assumed that a high number of EPs (≥6) might be a distinct subtype that required further investigation. In light of the present findings, we plan to further investigate the recurrence rates of patients with 2–5 EPs to determine the cutoff value of the EP number that predicts patients at high risk of recurrence.

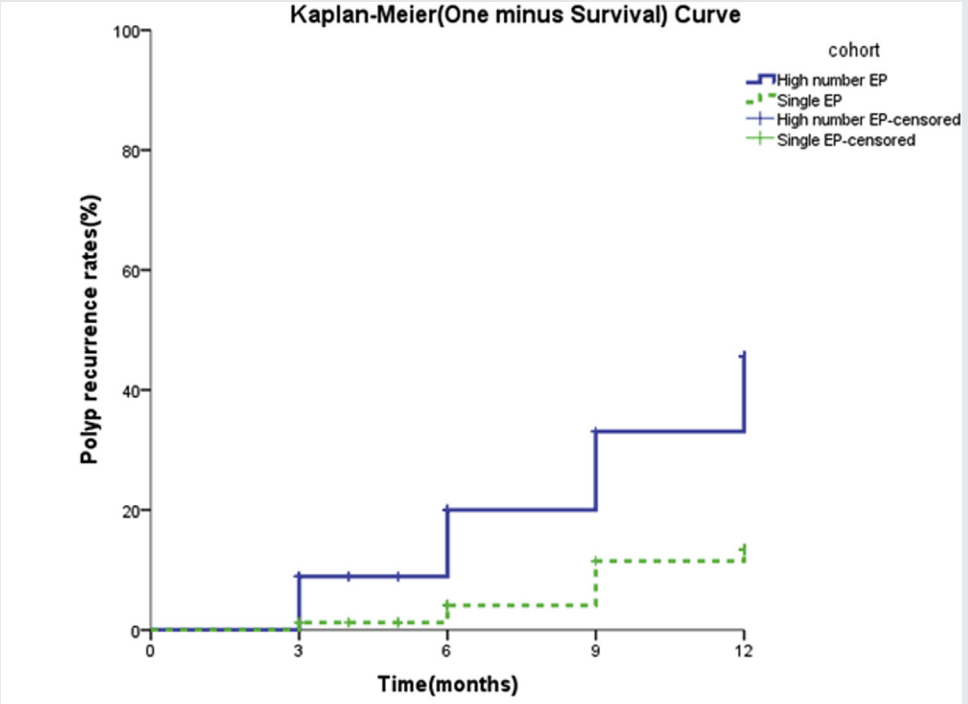
EP is a condition that has been attributed to infertility due to abnormal bleeding or presenting an unfriendly environment for embryo implantation. The interaction between an embryo and a receptive endometrium is a critical part of implantation, and it is thought that intrauterine abnormalities, such as EP, leiomyoma, or adhesion, may perturb implantation and cause infertility or early pregnancy loss (3, 4). Among these intrauterine lesions, EP is suggested to be the most common pathologic finding detected by office hysteroscopy for subjects with recurrent implantation failure (5), and it is recommended that EPs be removed in women seeking pregnancy (12, 23). However, some patients are more prone to EP recurrence than others; accordingly, they may have to undergo several polypectomy procedures before achieving pregnancy, which is painful and costly. Therefore, we must identify the population at high risk of EP recurrence while providing preoperative counseling and perform possible prevention measures to lower the recurrence rate.

The findings from our study shed light on clinical counseling and guiding decision making for patients with EP. Subjects with a high number of EPs should be well informed of the frequency of recurrence, and their postoperative management should be strengthened. From a clinical point of view, women with a high number of EPs should be instructed to achieve pregnancy as soon as possible after polypectomy before recurrence occurs. Subjects in reproductive medical centers should receive embryo transfer the next month after polypectomy, or extra preventive therapy, such as oral contraceptive pills and GnRH agonists, should be provided to prevent EP recurrence (24). For subjects who are on birth control, oral contraceptive pills as well as a levonorgestrel intrauterine device might be preferable because they inhibit endometrial overgrowth and decrease the risk of EP recurrence (24).

Concerning other predictive risk factors associated with EP recurrence, our data agreed with Wang et al.'s results that endometriosis was an independent risk factor for EP recurrence (25). The intrinsic factors might be that both endometriosis and EP exhibit endometrial overgrowth because of the alterations of expression patterns of estrogen receptor and aromatase (26). Moreover, increased proliferation and decreased apoptosis in the eutopic endometrium of women with endometriosis could facilitate EP formation (27, 28). The other associated risk factor was a history of polypectomy, indicating that some patients might have a polypoid background in the endometrium arising from genetic aberrations that are more vulnerable to developing EP (29). Age, BMI, leiomyoma, infertility, and PCOS status are well known risk factors for polyp development (11). However, they seemed to play an insignificant role in polyp recurrence in our study, which was consistent with Paradisi et al.'s results (13).

The pathophysiology of EP remains various and elusive. Proposed mechanisms that may contribute to EP development

FIGURE 2



Cumulative recurrence rates at each time point of two cohorts

	3 months	6 months	9 months	12 months
High number of EP	8.9% (3.4-14.4%)	20.0% (11.6-28.4%)	33.1% (22.5-43.7%)	45.5% (33.9-57.0%)
Single EP	1.2% (-1.2-3.6%)	4.1% (-0.4-8.6%)	11.5% (3.5-19.5%)	13.4% (4.6-22.2%)

Polyp recurrence rates of the two cohorts over the 1-year follow-up. Values are rate (95% confidence interval). EP = endometrial polyp.

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include localized E_2 overproduction (30), imbalanced expression of estrogen and progesterone receptors (31), deficient apoptosis (32), inflammatory status (33, 34), abnormal expression of growth factors (35), and even bacterial infection (36). However, mounting evidence has demonstrated pathogenic heterogeneity in the development of particular EP types (19, 37, 38). Our findings, if substantiated by future studies, may suggest that the significantly different prognosis of single and diffused growth of EP may be attributed to different mechanisms. Patients with a high number of EPs may comprise a distinct subtype that arises by an etiology different from the common EP and presents a disturbed endometrial milieu destined for the progression to more sinister pathologies. Therefore, it will be very interesting to investigate the intrinsic genetic background of this case type with the use of genome sequencing and perhaps develop specific preventive medications in the future.

The strength of our study lies in its prospective design and 1-year rigorous follow-up schedule of checks every 3 months after the initial surgery to identify the exact recurrence time. To our knowledge, this is the first prospective study that conducted a close follow-up in reproductive-age patients after polypectomy in a short period of time. It was astonishing to find that the recurrence events occurred very quickly in the high number of EP subgroup. A total of ten out of 182 patients had EP recurrence 3 months after surgery; of those ten, nine were from the high number of EP cohort. Six months after surgery, 20% of patients in the high number of EP cohort versus 4.1% of those in the single-EP cohort had EP recurrence. This result implied that the frequency of EP recurrence was higher than estimated in women of child-bearing age and that patients with excessive growth of multiple EPs will be at a particularly high risk of polyp recurrence very soon after polypectomy.

The lack of histologic confirmation of the TVCD diagnosis of recurrence was considered to be a limitation. Although hysteroscopy and guided biopsy are the criterion standards for diagnosis, it is an invasive examination that is not suitable for frequent follow-ups in a short period of time. Therefore,

TABLE 2

Risk factors for recurrence of EP after univariate and multivariate analysis.

Characteristic	HR (95% CI)	*P* value
Univariable analysis		
Age (y)	0.96 (0.90–1.03)	.27
BMI (kg/m^2)	1.00 (0.88–1.13)	.97
Multigravida	0.75 (0.32–1.72)	.49
Multipara	1.10 (0.60–2.00)	.94
PCOS	1.14 (0.16–8.37)	.90
Polyp size (cm)	0.58 (0.21–1.61)	.32
Leiomyoma	0.74 (0.26–2.10)	.57
Adenomyosis	2.09 (0.81–5.40)	.13
Endometriosis	2.09 (1.00–4.35)	.05
Previous polypectomy	3.41 (1.62–7.19)	< .001
High number of EPs vs. single EP	4.82 (2.00–11.63)	< .001
Infertility	1.64 (0.83–3.27)	.16
Multivariable analysis		
High number of EPs vs. single EP	3.45 (1.41–8.47)	< .01
Previous polypectomy	2.42 (1.13–5.41)	< .05
Endometriosis	2.18 (1.03–4.62)	< .05

Note: BMI = body mass index; CI = confidence interval; EP = endometrial polyp; HR = hazard ratio; PCOS = polycystic ovary syndrome.

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we chose TVCD, a noninvasive technique generally acceptable to the majority of patients with minimal discomfort, as a screening tool in our study. Furthermore, transvaginal ultrasonography is the first-line modality to detect polyps (2) with a good degree of accuracy when performed with high-resolution equipment by proficient practitioners (39). The sensitivity, specificity, positive predictive value, and negative predictive value of transvaginal sonography in detecting endometrial polyps were reported to be 86%, 94%, 91%, and 90%, respectively (40). With the use of TVCD, the diagnostic capability would be further improved, with a sensitivity reaching 97% (41). Last but not least, all ultrasound examinations were performed by a single expert physician (S.R.) to minimize potential error due to interobserver variability. Our research team plans to investigate long-term EP recurrence rate with the use of hysteroscopy as the criterion-standard diagnostic tool as the next step. Although the relatively short follow-up time is another study limitation, we recognize the need to identify recurrence potential soon after polypectomy, because our subjects were reproductive-age women likely waiting to conceive. Future studies should consider extending the follow-up period to demonstrate the complete recurrence rates of both cohorts and calculate the median recurrence-free survival times.

CONCLUSION

Findings from the present study indicate that reproductive-age patients with a high number of EPs are much more vulnerable to EP recurrence soon after polypectomy than those with a single EP. Patients with a high number of EPs, endometriosis, or a previous history of polypectomy may require increased monitoring and preventive methods for polyp recurrence.

The huge differences in prognosis between these two cohorts of patients suggest that patients with EPs that grow extensively around the uterus might comprise a distinct subtype that arises by a different etiology and pathogenesis. This study highlights the need for further research focusing on the etiology and mechanism of the development of this particular subtype of EP and its possible genetic background.

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REFERENCES

1. Mautter Gl NM, Robboy SJ. Endometritis, metaplasias, polyps, and miscellaneous changes. 2nd ed. Oxford: Churchill Livingston Elsevier; 2009.
2. Salim S, Won H, Nesbitt-Hawes E, Campbell N, Abbott J. Diagnosis and management of endometrial polyps: a critical review of the literature. J Minim Invasive Gynecol 2011;18:569–81.
3. Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, d'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev 2015:CD009461.
4. Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400–8.
5. Hosseini MA, Ebrahimi N, Mahdavi A, Aleyasin A, Safdarian L, Fallahi P, et al. Hysteroscopy in patients with repeated implantation failure improves the outcome of assisted reproductive technology in fresh and frozen cycles. J Obstet Gynaecol Res 2014;40:1324–30.
6. Al-Jefout M, Black K, Schulke L, Berbic M, Luscombe G, Tokushige N, et al. Novel finding of high density of activated mast cells in endometrial polyps. Fertil Steril 2009;92:1104–6.
7. Inagaki N, Ung L, Otani T, Wilkinson D, Lopata A. Uterine cavity matrix metalloproteinases and cytokines in patients with leiomyoma, adenomyosis or endometrial polyp. Eur J Obstet Gynecol Reprod Biol 2003;111:197–203.
8. Taylor HS. The role of HOX genes in human implantation. Hum Reprod Update 2000;6:75–9.
9. Taylor E, Gomel V. The uterus and fertility. Fertil Steril 2008;89:1–16.
10. Carneiro MM. What is the role of hysteroscopic surgery in the management of female infertility? A review of the literature. Surg Res Pract 2014;2014:105412.
11. Pereira N, Petrini AC, Lekovich JP, Elias RT, Spandorfer SD. Surgical management of endometrial polyps in infertile women: a comprehensive review. Surg Res Pract 2015;2015:914390.
12. Bosteels J, Weyers S, Puttemans P, Panayotidis C, van Herendael B, Gomel V, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 2010;16:1–11.
13. Paradisi R, Rossi S, Scifo MC, Dall'O' F, Battaglia C, Venturoli S. Recurrence of endometrial polyps. Gynecol Obstet Invest 2014;78:26–32.
14. Yang JH, Chen CD, Chen SU, Yang YS, Chen MJ. Factors Influencing the recurrence potential of benign endometrial polyps after hysteroscopic polypectomy. PLoS One 2015;10:e0144857.
15. Preutthipan S, Herabutya Y. Hysteroscopic polypectomy in 240 premenopausal and postmenopausal women. Fertil Steril 2005;83:705–9.
16. Gao W, Zhang L, Li W, Li J, Wang W, Zhao W, et al. Three-year follow-up results of polypectomy with endometrial ablation in the management of endometrial polyps associated with tamoxifen in Chinese women. Eur J Obstet Gynecol Reprod Biol 2012;161:62–5.
17. AlHilli MM, Nixon KE, Hopkins MR, Weaver AL, Laughlin-Tommaso SK, Famuyide AO. Long-term outcomes after intrauterine morcellation vs. hysteroscopic resection of endometrial polyps. J Minim Invasive Gynecol 2013;20:215–21.
18. Crum CP, Hornstein MD, Nucci MR, Mutter GL. Hertig and beyond: a systematic and practical approach to the endometrial biopsy. Adv Anat Pathol 2003;10:301–18.

19. Wong M, Crnobrnja B, Liberale V, Dharmarajah K, Widschwendter M, Jurkovic D. The natural history of endometrial polyps. Hum Reprod 2017; 32:340–5.
20. Valentin L. Imaging techniques in the management of abnormal vaginal bleeding in nonpregnant women before and after menopause. Best Pract Res Clin Obstet Gynaecol 2014;28:637–54.
21. Henriquez DD, van Dongen H, Wolterbeek R, Jansen FW. Polypectomy in premenopausal women with abnormal uterine bleeding: effectiveness of hysteroscopic removal. J Minim Invasive Gynecol 2007;14:59–63.
22. di Spiezio Sardo A, Calagna G, Scognamiglio M, O'Donovan P, Campo R, de Wilde RL. Prevention of intrauterine post-surgical adhesions in hysteroscopy. A systematic review. Eur J Obstet Gynecol Reprod Biol 2016;203:182–92.
23. American Association of Gynecologic Laparoscopists. AAGL practice report: practice guidelines for the diagnosis and management of endometrial polyps. J Minim Invasive Gynecol 2012;19:3–10.
24. Indraccolo U, di Iorio R, Matteo M, Corona G, Greco P, Indraccolo SR. The pathogenesis of endometrial polyps: a systematic semi-quantitative review. Eur J Gynaecol Oncol 2013;34:5–22.
25. Wang N, Zhang Y, Liu B. Demographic and clinical features of endometrial polyps in patients with endometriosis. Biomed Res Int 2016;2016:1460793.
26. de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet 2010;376:730–8.
27. Dmowski WP, Ding J, Shen J, Rana N, Fernandez BB, Braun DP. Apoptosis in endometrial glandular and stromal cells in women with and without endometriosis. Hum Reprod 2001;16:1802–8.
28. Park JS, Lee JH, Kim M, Chang HJ, Hwang KJ, Chang KH. Endometrium from women with endometriosis shows increased proliferation activity. Fertil Steril 2009;92:1246–9.
29. Tallini G, Vanni R, Manfioletti G, Kazmierczak B, Faa G, Pauwels P, et al. HMGI-C and HMGI(Y) immunoreactivity correlates with cytogenetic abnormalities in lipomas, pulmonary chondroid hamartomas, endometrial polyps, and uterine leiomyomas and is compatible with rearrangement of the HMGI-C and HMGI(Y) genes. Lab Invest 2000;80:359–69.
30. Maia H Jr, Pimentel K, Silva TM, Freitas LA, Zausner B, Athayde C, et al. Aromatase and cyclooxygenase-2 expression in endometrial polyps during the menstrual cycle. Gynecol Endocrinol 2006;22:219–24.
31. Peng X, Li T, Xia E, Xia C, Liu Y, Yu D. A comparison of oestrogen receptor and progesterone receptor expression in endometrial polyps and endometrium of premenopausal women. J Obstet Gynaecol 2009;29:340–6.
32. Taylor LJ, Jackson TL, Reid JG, Duffy SR. The differential expression of oestrogen receptors, progesterone receptors, Bcl-2 and Ki67 in endometrial polyps. BJOG 2003;110:794–8.
33. Carvalho FM, Aguiar FN, Tomioka R, de Oliveira RM, Frantz N, Ueno J. Functional endometrial polyps in infertile asymptomatic patients: a possible evolution of vascular changes secondary to endometritis. Eur J Obstet Gynecol Reprod Biol 2013;170:152–6.
34. Bozkurt M, Sahin L, Ulas M. Hysteroscopic polypectomy decreases NF-κB1 expression in the mid-secretory endometrium of women with endometrial polyp. Eur J Obstet Gynecol Reprod Biol 2015;189:96–100.
35. Ferrari G, Cook BD, Terushkin V, Pintucci G, Mignatti P. Transforming growth factor-beta 1 (TGF-beta1) induces angiogenesis through vascular endothelial growth factor (VEGF)–mediated apoptosis. J Cell Physiol 2009; 219:449–58.
36. Fang RL, Chen LX, Shu WS, Yao SZ, Wang SW, Chen YQ. Barcoded sequencing reveals diverse intrauterine microbiomes in patients suffering with endometrial polyps. Am J Transl Res 2016;8:1581–92.
37. Pal L, Niklaus AL, Kim M, Pollack S, Santoro N. Heterogeneity in endometrial expression of aromatase in polyp-bearing uteri. Hum Reprod 2008;23: 80–4.
38. Kitaya K, Tada Y, Taguchi S, Funabiki M, Hayashi T, Nakamura Y. Local mononuclear cell infiltrates in infertile patients with endometrial macropolyps versus micropolyps. Hum Reprod 2012;27:3474–80.
39. Shalev J, Meizner I, Bar-Hava I, Dicker D, Mashiach R, Ben-Rafael Z. Predictive value of transvaginal sonography performed before routine diagnostic hysteroscopy for evaluation of infertility. Fertil Steril 2000;73:412–7.
40. Vercellini P, Cortesi I, Oldani S, Moschetta M, de Giorgi O, Crosignani PG. The role of transvaginal ultrasonography and outpatient diagnostic hysteroscopy in the evaluation of patients with menorrhagia. Hum Reprod 1997;12:1768–71.
41. Jakab A, Ovari L, Juhasz B, Birinyi L, Bacsko G, Toth Z. Detection of feeding artery improves the ultrasound diagnosis of endometrial polyps in asymptomatic patients. Eur J Obstet Gynecol Reprod Biol 2005;119:103–7.