

## Review

# Critical Aspects of Endometrial Polyp Clinical Management: A Narrative Review

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## Abstract

**Objective:** Endometrial polyps are one of the most often diagnosed gynecological pathologic findings, affecting women from reproductive age to advanced menopause. In women of childbearing age, they can cause infertility, although a clear cause-and-effect relationship is not always evident. In postmenopausal women, endometrial polyps may manifest primarily with abnormal uterine bleeding (AUB). They are usually benign lesions, and the malignant transformation, especially in menopausal women, occurs infrequently increasing with age. The ultrasound suspicion of an endometrial polyp requires a better definition of its size, position, and nature through hysteroscopy. Hysteroscopy performed as an outpatient procedure, in addition to diagnosis may be followed by the simultaneous removal of the polyp (see & treat approach). If this is not possible in an outpatient setting, polypectomy can be performed in the operating theatre by means of resectoscopy or mechanical hysteroscopic tissue removal (mHTR) system. This critical study about the management of endometrial polyps, intends to examine what is still being discussed in this regard. **Mechanism:** A narrative review was conducted analyzing the available literature regarding the management of endometrial polyps in infertile childbearing age and pre and postmenopausal women. **Findings in Brief:** There is no agreement that all endometrial polyps should be removed. Polyps <10 mm can be monitored over time. In infertile women, polypectomy is recommended because it is a possible impediment to fertilization, or for Assisted Reproductive Technology (ART) procedures, however not all studies are of agreement. For patients with polyps symptomatic of AUB, polypectomy must always be recommended. **Conclusions:** Following an endometrial polyp diagnosis by hysteroscopy, the decision to operate should be considered for infertile women or for those with large or symptomatic menopausal polyps. Due to the lack of clear guidelines, the decision can be postponed by adopting careful surveillance in some cases.

**Keywords:** endometrial polyp; endometrial polypectomy; infertility; abnormal uterine bleeding; hysteroscopy; resectoscopy; mechanical hysteroscopic tissue removal system

## 1. Introduction

Endometrial polyps are localized outgrowths occurring anywhere within the uterine cavity. They contain a variable number of glands, stroma, and blood vessels. A single or more polyps can be diagnosed in the uterine cavity, they can be pedunculated or with a large base, just a few millimeters in size, or big enough to fill the whole uterine cavity [1]. The incidence of endometrial polyps is unknown, because many of them are asymptomatic and is dependent on the population studied [2]. Among sub-infertile women, prevalence has been estimated up to 32% [2,3]. In patients with unexplained infertility, the frequency of hysteroscopic diagnosis of endometrial polyps has been reported as being between 16.5% and 26.5%, in infertile patients who suffered from endometriosis it is up to 46.7%, and in those suffering from recurrent pregnancy loss it is estimated between 0.6 to 5% [4,5].

In pre and postmenopausal age, polyps may occur mainly with abnormal uterine bleeding (AUB), which is the most common symptom, present in 10%–40% of cases [3,6,7]. Although most endometrial polyps are benign,

studies report they may become hyperplastic, with malignant transformation developing in up to 12.9% of cases [3,8]. Numerous hypotheses concerning the onset of endometrial polyps have been suggested including inflammatory, genetic, and familial hereditary factors. Conditions of imbalanced hyperestrogenism, obesity, polycystic ovary syndrome (PCOS), late menopause, estrogen secreting gonadal stromal tumors, and chronic liver disease have been suggested as endocrine causes. Among iatrogenic causes, an increased exogenous unbalanced estrogen administration, and a tamoxifen or toremifene treatment for breast cancer has been considered [2,3,9]. Postmenopausal patients taking tibolone are three times as likely to suffer from endometrial polyps [10].

Endometrial polyps are sometimes detected in asymptomatic patients by transvaginal ultrasound (TVU). At TVU endometrial polyps appear in most cases as a localized, defined, hyperechoic thickening of the endometrium, in some cases with multiple areas of hypoechogenicity, as a non-specific endometrial thickening, or focal mass within the endometrial cavity [11]. Doppler fluximetry is often capable of identifying the vascular axis of the polyp. Sonohys-



terography has excellent sensitivity assessing the size and location of an endometrial polyp [11–13]. Hysteroscopy is the gold standard for the diagnosis of endometrial polyps. It provides the number and characteristics of a polyp's implantation base (sessile or pedunculated), their size, location, and texture, which are all additional clinical information useful for the proper hysteroscopic operative approach. Dilation and Curettage (D&C), combined with the use of polypectomy forceps, should be avoided due to inaccuracy for the diagnosis and management of endometrial polyps [12].

Endometrial polyps are usually soft, but sometimes they can be hard and semi-myomatous (adenomyomatous forms). Functional polyps are characterized by their similarity to the adjacent endometrium, while an irregular surface, with areas of inflammation and/or necrosis, possible presence of glandular architectural abnormalities (with glandular cystic or otherwise) is highly indicative of endometrial hyperplasia associated with polyps. An evident, tortuous, superficial vascularization can be indicative of atypical features in the endometrial polyp.

In office hysteroscopy may be followed by the immediate removal of the polyp if its location, size, and patient clinical condition allow this (see & treat approach), or be completed by targeted biopsy [13,14]. For large polyps, or if the woman's clinical condition requires this, an operating room is necessary.

## 2. Material and Methods

Clinical aspects of endometrial polyps, such as infertility, AUB, risk of malignancy, together with polypectomy options have been examined in current literature to find answers to the following questions:

- Does the presence of an endometrial polyp always cause infertility?
- Should all infertile women with diagnosed endometrial polyps undergo polypectomy?
- Should the polyps be removed only if intrauterine insemination (IUI) or *in vitro* fertilization-embryo transfer (IVF-ET) is planned?
- In menopausal women, should all endometrial polyps, even if asymptomatic for AUB and sometimes accidentally diagnosed, be removed?
- For the above patients, does the presence of risk factors for endometrial cancer (obesity, diabetes, hypertension, tamoxifen treatment, hormone replacement therapy) indicate the need for polypectomy?
- If patients complain of AUB, due to the risk of malignant transformation, should polypectomy be offered anyway?
- How can the presence of small polyps be monitored if polypectomy is not deemed necessary?
- When an endometrial polypectomy is planned, where and how is the procedure best performed (in office or operating theatre)?

- What are the factors by which this decision is made?

The size, the position, the number of polyps?

Other factors may influence the choice of how the polypectomy should be performed, such as a woman's clinical condition, the availability of all types of instrumentation (operative hysteroscope, mechanical instruments, electrodes, mechanical Hysteroscopic Tissue Removal (mHTR) system, resectoscopes), the surgeon's experience of working in an office rather than in an operating room setting. Finally, financial considerations on the cost-effectiveness of the procedure are of paramount importance to determine the setting for the polypectomy. In all these critical aspects of the management of endometrial polyps we have focused our attention by trying to define decision points we consider to be indispensable.

## 3. Results

Data in literature suggest a relationship between endometrial polyps and infertility, with an increased pregnancy rate after polypectomy (15–24%) in women with no other causes of infertility [4,5,12,15]. Nevertheless, the lack of randomized trials makes it difficult to draw a conclusion regarding the potential role of endometrial polypectomy in increasing pregnancy rates in infertile women. No difference was found in the pregnancy rates after a hysteroscopic polypectomy for small polyps ( $\leq 10$  mm) compared to larger or multiple ones [16]. The rate of pregnancy after the polyp removal was 57.4% for women with endometrial polyps near the tubal ostium, and 40.3% for multiple polyps suggesting that the location and number influence pregnancy rates [17]. The cumulative clinical pregnancy rate following IUI cycles was higher for women who underwent polypectomy compared to women with remaining polyps, or who underwent polyp biopsy only [5,18]. In a systematic review regarding hysteroscopic polypectomy, compared with no treatment, and Assisted Reproductive Technology (ART) outcomes, eight studies were analyzed [19]. The polypectomy resulted in an increased rate of clinical pregnancy in patients who underwent IUI, but no clear advantages for clinical pregnancy, live birth, miscarriage, or implantation rates in patients who underwent *in vitro* fertilization (IVF) were found [19]. Retrospective studies comparing IVF or Intra Cytoplasmic Sperm Injection (ICSI) cycles in women who underwent embryo transfer (ET) without polypectomy concluded, that endometrial polyps did not influence pregnancy and implantation results in a negative way, especially for polyps  $< 20$  mm. Nevertheless, a trend for greater pregnancy loss for patients without endometrial polypectomy was observed [20–23].

The indication to remove endometrial asymptomatic polyps in pre or postmenopausal patients is controversial. The diagnosis of small and asymptomatic endometrial polyps does not necessitate immediate surgery, and a conservative management may be considered due to the possibility of regression of polyps up to 25% and the low inci-

dence of finding a malignancy [2,24]. Polypectomy might be an overtreatment, because the patient must be anesthetized in the operating room, with surgical risks and economic commitment [9,25]. AUB usually is more frequently seen in premenopausal women and occurs in about 25% of symptomatic postmenopausal women. AUB is greatly linked to patient's hyperestrogenic state and not to the polyp itself, even if large polyps may directly account for bleeding due to an ulceration of the endometrium. Moreover, some women could be completely asymptomatic or show intermenstrual or postcoital spotting because of the presence of cervical polyps [6,24,25]. In postmenopausal women, AUB can vary greatly due to the characteristics of the polyp (number, size, and vascularity), and the association with an increased risk of malignant transformation [6]. Two recent meta-analyses showed that the prevalence of premalignant and malignant lesions in patients with endometrial polyps is estimated at 1.1% in premenopausal, and between 3.4% and 4.9% in postmenopausal women [26,27]. A review by Uglietti *et al.* [26] concerning the risk of endometrial cancer, which included 51 studies (35,345 patients) on pre or postmenopausal patients with AUB or preoperative diagnosis of benign-looking endometrial polyps (at TVU or at hysteroscopy), found that the prevalence of malignant polyps was 2.73% (95% confidence interval [CI] 2.57–2.91), however with different conclusions reached by the various studies included. Indeed, lower rates were observed for premenopausal (1.12%) than for postmenopausal women (4.93%), with a statistically significant difference (Chi-square = 397.21,  $p < 0.0001$ ). The risk of developing malignancy was higher among women with vaginal bleeding (5.14%) rather than asymptomatic ones (1.89%) (Chi-square = 133.13,  $p < 0.001$ ). In a systemic review and meta-analysis by Sasaki *et al.* [28], regarding factors associated with malignant transformation in removed endometrial polyps in 37 studies (comprising 21,057 patients), reported that the prevalence of premalignant and malignant lesions was 3.4% (95% CI 2.8–4.1). AUB, menopausal status, age >60 years, diabetes mellitus, PCOS, hypertension, obesity, and tamoxifen treatment were associated with endometrial polyp malignant transformation. Breast cancer, hormonal therapy, parity, and endometrial polyp size were not associated with malignancy of endometrial polyps [28–32].

The frequency of atypical or malignant features within endometrial polyps in infertile women has also been evaluated [33]. Diffuse polypoid appearance of the endometrial cavity, high body mass index (BMI), and the duration of infertility, were predictors of endometrial atypical or malignant features within polyps detected in infertile patients undergoing office hysteroscopy [33].

Hysteroscopy is the gold standard procedure for the diagnosis and treatment of endometrial polyps. Carugno *et al.* [34] defined the office setting as appropriate if pain can be controlled without the need for anesthesia or with conscious sedation, otherwise the operating room should be

the first choice. Several hysteroscopic techniques for endometrial polypectomy have been described, but there are no comparative studies among these methods regarding efficacy, feasibility, and cost [6,25]. Small polyps (<0.5 cm) can be removed with 5-Fr mechanical instruments (scissors and/or grasping forceps). Larger polyps (>0.5 cm) can be removed en bloc (by resecting the implantation base of the lesion with scissors or bipolar electrode) only if the internal uterine orifice (IUO) is large enough to allow them to be removed. In 2002, Bettocchi *et al.* [14] described the technique for removal of large endometrial polyps  $\geq 20$  mm, with a disposable bipolar electrode cutting the polyp in thin slices in an office setting. Due to technical difficulties and the need for surgical skill, large polyps ( $\geq 20$  mm) are generally not considered suitable for removal in the office and require treatment in the operating room with a resectoscopic approach [25]. Resectoscopes of different diameters (from 9 mm, 27-Fr, to 5 mm, 15-Fr) and with different electrosurgical energy (monopolar or bipolar) can be used. The risks associated with intravasation are greater when nonconductive solutions (glycine or mannitol/sorbitol) are utilized for monopolar resectoscopes as distensive fluids. When using bipolar resectoscopes with normal saline as a distending medium, the risks of fluid intravasation is minimized, although it may occur for fluid deficit over 1.5 L [35]. These instruments might require dilation of the cervix to approximately 8–10 mm, and perforation of the uterus (rate estimated at <1%) can occur with cervical dilators, mechanical grasping instruments or the resectoscopic system itself [36]. Major resectoscopic adverse events have also included damage to abdominal tissues and organs [36]. Recently miniaturized bipolar resectoscope (5 mm in diameter), comparable in its design to an ambulatory continuous flow hysteroscope, have been released reducing the need for cervical dilatation and complications [37]. An innovative minimally mHTR system has been developed to overcome the limits of resectoscopic procedures. Saline solution is used to distend the cavity and no fluid overload occurs. Aspiration of the tissue fragments by the mHTR system ensures a clear view, allows the histological examination of all the fragments, meaning there was no necessity to employ additional equipment to remove tissue residue [38,39]. This system is well suited for the removal of endometrial polyps, regardless of location and size with no damage to the endometrium [40]. The introduction of miniaturized mHTR systems (5.5 mm to 6.3 mm in diameter) has enabled these newer, smaller devices to be used in an office environment [38,41]. Recent studies confirm the truly minimally invasive and safe treatment offered by mHTR systems for endometrial polyps  $\geq 20$  mm in size having a shorter procedure time than those treated with loop or bipolar electrode resection in an operating room, or in an office setting [38,42–46]. The mHTR system polypectomy has been recognized as an effective procedure completed in almost one third of the usual time with less reliance on the surgeon's skill [42,43].

## 4. Discussion

### 4.1 Endometrial Polyp Management in Childbearing Age Patients

It is believed that polyps play a role in hindering embryo implantation, even if this is not yet clear. Endometrial polyps could affect implantation as they are lesions which take up space, or because they may be the cause of inflammatory changes. It has been observed that in patients with endometrial polyps the activated mast cells number is seven-times higher during the menstrual cycle in the uterine cavity [47]. The activated mast cells play a key role in inflammatory processes releasing substances such as histamine, prostaglandin, leukotrienes, and cytokines, that might interfere with the physiological implantation of the embryo [48]. A case-control study investigated the expression of HOXA10 and HOXA11, molecular markers of endometrial receptivity. The study revealed a marked reduction in HOXA10 and HOXA11 messenger RNA levels in presence of endometrial polyps, which could result in implantation failure. Endometrial polypectomy in infertile women is justified by these findings, as a molecular mechanism could support the reduced pregnancy rates in patients with endometrial polyps [49]. Up to now, there is no common position on whether endometrial polyps should be removed in infertile women before attempting a natural, or by ART procedures pregnancy [50,51]. The true clinical significance of endometrial polyps on fertility is in question, so an expectant conduct is contemplated by most studies in women planning to undergo IVF [20–22].

For these reasons, some conclusive considerations can be drawn taking into account that sometimes a personalized treatment should be proposed:

- Criteria to define the size of polyps, which should be removed or monitored, have not yet been determined. It must be considered that endometrial polyps <10 mm sometimes vanish naturally [24,52].

- Women who are unable to become pregnant for unknown reasons, may be advised to undergo endometrial polypectomy [12,53].

- When diffuse polypoid appearance of the endometrial cavity is detected during office hysteroscopy, guided hysteroscopic resection should be performed [33].

- Endometrial polypectomy should be considered by infertile patients planning to undergo IUI, even if only one prospective randomized study confirms this clinical management [5].

- In women intending to undergo IVF, no strong evidence supports endometrial polypectomy to increase the pregnancy rate [20–23]. For repeated failed IVF attempts, endometrial polypectomy is justified, although further studies are necessary to verify the increase of the pregnancy rate [53].

Regarding cost-analysis data of removing polyps, a systematic review found that hysteroscopic endometrial

polypectomy (in an office or operative theatre setting) was clinically significant and cost-effective when performed before IUI or IVF [54].

### 4.2 Management of Endometrial Polyps in Pre or Postmenopause Women

Data are too scarce to establish if the removal of small, fibroglandular polyps could be a lifesaving and cost-effective procedure in pre or postmenopausal asymptomatic women. Data does not support the benefits to recommend all endometrial polypectomies in postmenopausal women as a strategy to prevent malignant degeneration [12]. In these cases, a watchful waiting approach should be carefully discussed with the patient since the presence of endometrial polyps can lead to anxiety about malignancy, occurring in 0–12.9% of cases in series reported to date [3,8]. Physicians should inform patients with any clinical risk factors (aged  $\geq 60$  years, postmenopausal state, AUB, hypertension, diabetes mellitus, obesity, PCOS, polyp size >2.2 cm, multiple polyps, and tamoxifen use) about the possibility of having premalignant or malignant polyps compared with the general population, and the necessity to undergo an endometrial polypectomy [28,55]. Based on these results, patients to undergo endometrial polypectomy could be selected by offering the others a careful surveillance [26,32]. In patients on estrogen replacement therapy or on tamoxifen treatment for breast cancer, the levonorgestrel intrauterine system (LNG-IUS) has been proposed to prevent the development of endometrial polyps and hyperplasia [55]. The LNG-IUS has also been used for the regression of endometrial polyps in a controlled not randomized study [56]. Obesity is a risk factor for endometrial premalignancy/malignancy in polyps being associated with higher estrogen levels due to androgen conversion by increased aromatase levels in visceral fat [30,31]. Besides this, both insulin resistance and hyperinsulinemia occurring in obese women could justify the association between obesity and a greater risk of endometrial premalignancy/malignancy [32]. PCOS is associated with a higher risk of premalignant and malignant endometrial polyps in premenopausal women. Therefore, an hysteroscopic polypectomy should be offered to PCOS patients diagnosed with endometrial polyps regardless of symptoms [57]. A cohort study reported that endometrial polyps and endometrial cancer may be present in the same woman, and that premalignant changes occasionally present in endometrial polyps are the same as those observed in atypical endometrial hyperplasia [58]. Since atypical hyperplasia and endometrial cancer can result from endometrial polyps, any blind techniques for excision of endometrial polyps such as D&C should be avoided. Elyashiv *et al.* [59], in a class II study, revealed that when an atypical hyperplasia or a carcinoma was found in the polyps, a residual atypical endometrial hyperplasia or carcinoma was present in the 88% of hysterectomy specimens, mostly (55.6%) as multifocal le-

sions. In these cases, hysterectomy as first-line therapeutic option is recommended [58,59].

Considering the available evidence, in pre- or postmenopausal women suffering of an endometrial polyp, the following recommendations can be suggested:

- Endometrial polypectomy for small asymptomatic polyps (<2 cm) in postmenopausal women is not cost-effective.

- Endometrial polypectomy must be recommended in postmenopausal women, for large polyps (>2 cm), or for known endometrial carcinoma risk factors.

- Regardless of the size of an endometrial polyp, if patients who complain of AUB, due to the risk of malignancy, endometrial polypectomy should be offered in any case.

- Hysterectomy with bilateral salpingo-oophorectomy is indicated in postmenopausal and in premenopausal women with a carcinoma diagnosed on an endometrial polyp.

- Postmenopausal women with atypical hyperplasia because of the risk of underlying malignancy or progression to cancer, should undergo a total hysterectomy and a bilateral salpingo-oophorectomy.

- For premenopausal women with atypical hyperplasia diagnosed on an endometrial polyp, a total hysterectomy without salpingo-oophorectomy could be enough, and a bilateral salpingectomy should be considered as this may reduce the risk of a future ovarian malignancy, as indicated by Green-top Guideline No.67 of the Royal College of Obstetricians and Gynaecologists (RCOG) /the British Society for Gynaecological Endoscopy (BSGE) [60].

#### 4.3 Conservative Management of Endometrial Polyps with Atypical Focal Hyperplasia in Childbearing Patients

In fertile women who wish to become pregnant, polyps with concurrent focal atypical hyperplasia can be treated conservatively. A polypectomy with the resectoscope, also removing the endometrium surrounding the base of polyp implantation, followed by subsequent hormone therapy is considered to be the first-choice treatment [1]. This conservative and minimally invasive approach has a good overall therapeutic efficacy, if the polyp implantation base and the surrounding areas are free from disease, and no doubt remains concerning the multifocality of atypical hyperplasia [6,28].

#### 4.4 Endometrial Polypectomy

The vaginoscopic approach, using miniaturized operative hysteroscopes (4 mm or 5 mm in size), has contributed to the widespread diffusion of hysteroscopy as an office procedure with minimal discomfort, high patient acceptance and low complication rate. The endometrial polypectomy in office, or in outpatient clinic shows many advantages such as reduced anesthesiologic risks, enhanced time, and cost-effectiveness, with lower economic commitment [14]. There are no guidelines regarding size, location, and number of polyps beyond which polypectomy should be

performed in an operating theatre. It is not only the characteristics of the polyp (size and location) that determine the best clinical setting to perform endometrial polypectomy. Large, pedunculated polyps may be removed easily in a pluriparous patient immediately after diagnosis in the office, but polyps of a few millimeters located near the tubal ostium in a postmenopausal nulliparous patient may require the operating room, due to the pain evoked by passing the hysteroscope through the IUO. The decision regarding where and how to undertake hysteroscopic procedures depends on several factors including the available infrastructure (staffing, equipment, facilities), preferences (both patient and clinician), the availability of various type of instruments, difference of energy (mechanical or electric) and diameter (from less than 4 mm to 9 mm), the type of diagnostic and operative procedures), and health economics (i.e., reimbursement, investment, and cost-effectiveness). Specific clinical conditions (heart disease, severe hypertension, anxiety, vagal vessel syndrome, *etc.*) may require sedation of the patient. The use of resectoscopes, even if with a reduced diameter (5 mm, 15 Fr) and with a bipolar electrosurgical energy, require great skill and a long learning curve on the part of the surgeon for chip removal, difficult visualization, and repeated in-and-out movements [25]. The small diameter resectoscopes have reduced the need for cervical dilatation and the complication rate [37]. The mHTR systems avoid the complications of resectoscopic procedures due to electrosurgical energy, as well as thermal damage and mechanical action. This system allows the surgeon to carry out the polypectomy in a safer, faster, and effective manner when compared to conventional resectoscopy [38].

## 5. Conclusions

The diagnosis of endometrial polyps is a frequent gynecological condition increasing with age. Their diagnosis, suspected with TVU, must be confirmed by hysteroscopy. After the diagnosis the decision on polypectomy should be considered for infertile women or for those with large or symptomatic menopausal polyps. Due to the lack of clear guidelines, a correct communication must also take place with the patient regarding the clinical significance of endometrial polyps, the setting of the procedure, possible complications and in some cases, the decision can be postponed by adopting careful surveillance.

## Author Contributions

ORC and MF designed and performed the research. ORC and MF analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. Both authors read and approved the final manuscript.

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