Recurrent endometrial polyps – influencing factors and treatment

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Abstract

An endometrial polyp (EP) is a frequently encountered gynecologic disease, and the two main symptoms are abnormal uterine bleeding and infertility. Hysteroscopic polypectomy is an effective method to remove them. The postoperative polyp recurrence might result in the reappearance of abnormal uterine bleeding or infertility. There is limited data on the factors that influence postoperative recurrence. Progesterone appears to be a valid therapeutic alternative for the management of recurrent endometrial polyps. Levonorgestrel intrauterine device is not an option for women who want to conceive. Infertile women should be counseled to achieve a pregnancy in the next couple of months after hysteroscopic polypectomy, and as soon as possible before polyp recurrence.

Keywords: *recurrent endometrial polyps, infertility, hysteroscopy*

Rezumat

Polipii endometriali (PE) sunt frecvent întâlniți în practica ginecologică, motivele prezentării la medic fiind cel mai adesea infertilitatea și sângerarea uterină anormală. Polipectomia histeroscopică este considerată standardul de aur pentru tratamentul PE. Recurența postoperatorie determină reapariția simptomatologiei. Factorii care influențează recurența PE sunt puțin cunoscuți. Progesteronul este o metodă terapeutică eficientă de prevenire a reapariției PE. Steriletul cu levonorgestrel nu este o metodă utilă în cazul pacientelor infertile care își doresc o sarcină. Femeile cu infertilitate trebuie consiliate să obțină o sarcină în următoarele luni după polipectomia histeroscopică.

Cuvinte-cheie: *recurența polipilor endometriali, infertilitate, histeroscopie*

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Introduction

When talking about the evaluation of the uterine cavity, hysteroscopy is considered to be the gold standard[(1)]. Hysteroscopy is a diagnostic and an operative procedure and evaluates the intrauterine pathology in premenopausal and postmenopausal women. Hysteroscopy is indicated in the workup of infertile patients with suspected uterine abnormalities and in patients complaining of abnormal uterine bleeding[(2,3)]. Millions of women present each year to gynecologists accusing abnormal uterine bleeding. Abnormal uterine bleeding can be caused by structural abnormalities (such as endometrial polyps), ovulatory dysfunctions coagulopathies or due to iatrogenic causes[(4-6)]. Endometrial polyps are one of the most common causes of abnormal uterine bleeding and infertility, but they can also be asymptomatic[(7)]. They have a low potential for malignancy: 1-2% of lesions in premenopausal women and 4-5% of lesions in postmenopausal women[(8-11)].

Endometrial polyps (EP) are epithelial proliferations that comprise a variable vascular, glandular, fibromuscular and connective tissue components. They are hyperplastic overgrowths of endometrial glands and stroma that form a projection from the surface of the endometrium[(12)].

Endometrial polyps can be diagnosed by ultrasound, sonohysterography, hysteroscopy and uterine curettage. Among them, hysteroscopy is superior to the other three methods, because it is able to detect the number, the type and the location of endometrial polyps. After diagnosis, hysteroscopic polypectomy is now the gold standard for treatment. Histeroscopy allows the direct visualization and the complete excision of the polyp and keeps the adjacent endometrium intact. For infertile women with no other reason to explain their infertility, hysteroscopic polypectomy improves fertility and increases pregnancy rates[(13-16)].

The postoperative polyp recurrence might determine the reappearance of abnormal uterine bleeding or infertility. What can we do when facing a woman with recurrent endometrial polyps?

Histopathology

Single or multiple polyps may occur and range in diameter from a few millimeters to several centimeters. Polyps can develop anywhere in the uterine cavity. Endometrial polyps may be hyperplastic, functional, atrophic or mixed endocervical-endometrial. Endometrial polyps share some histologic characteristics: a polypoid

configuration with surface epithelium on at least three sides, a central (usually fibrotic) core that occasionally contains smooth muscle, irregular glandular architecture (often dyssynchronous with adjacent normal endometrium) and thick-walled vessels.

Hyperplastic polyps are most likely related to hormonal imbalances and are composed of proliferating, irregularly-shaped glands resembling endometrial hyperplasia. Atrophic polyps have a glandular architecture and are typically seen in postmenopausal women. In functional polyps, the glands are in synchrony with those of the endometrium. Tamoxifen-related endometrial polyps are usually multiple and their microscopic features usually include hyperplastic glands[17-21].

Etiology, incidence and presentation of endometrial polyps

The etiology of endometrial polyps is not exactly known. The close relationship with the background endometrium suggests a similar way in which they proliferate and express apoptosis-regulating proteins during the menstrual cycle[22]. Endometrial polyps overexpress estrogen and progesterone receptors, while dropping their apoptotic regulation. This mechanism is similar in both pre- and postmenopausal women[23]. Several molecular mechanisms try to explain the development of endometrial polyps: monoclonal endometrial hyperplasia, overexpression of endometrial aromatase, and gene mutations[24-26]. The etiology and the pathogenesis of polyps in obese females appear to be associated with the progesterone receptor, the inhibition of apoptosis and cellular mechanisms linked with inflammation[27].

Endometrial polyps are one of the most common causes of abnormal uterine bleeding and infertility, but they can also be asymptomatic. Endometrial polyps can be an incidental finding during pelvic ultrasonography. Approximately 25% of symptomatic pre- and postmenopausal women have endometrial polyps. Menorrhagia may occur in 50% of the premenopausal women. Other presentations include postmenopausal bleeding, polyp externalization through the cervical ostium, abnormal vaginal discharge, and incidental bleeding during hormonal therapy[27,28].

The highest incidence of endometrial polyps is in the fifth decade of life and declines after menopause. This pathology is rare under the age of 20. Endometrial polyps are diagnosed in 24-41% of women with abnormal uterine bleeding and in 10% of asymptomatic women[29,30].

Influencing factors

1. Hormone replacement therapy and tamoxifen

A number of studies report an increased incidence of endometrial polyps in women on hormone replacement therapy (HRT) and tamoxifen. Tamoxifen acts as a selective modulator receptor and estrogen agonist on the endometrium[31]. The influence on endometrial polyps seems to be through estrogen, of which endometrial polyps depend. However, endometrial polyp formation appears to be related to the type and dosage of the estrogen and progestogen in HRT; in particular, a progestogen with high anti-estrogenic activity may have an important role in preventing the development of endometrial polyps[32]. One prospective cohort study of 248 consecutive patients confirmed tamoxifen as associated with endometrial polyps. The same study rejects the hypothesis that hormone replacement therapy is a risk factor for endometrial polyps[33]. Older studies support that endometrial polyps are less common in women on continuous combined HRT, but their appearance has been reported. Rarely, women reporting incidental bleeding after having achieved prolonged amenorrhea on continuous combined HRT will be found to have an endometrial polyp. Such cases always impose biopsy and histological evaluation, because adenocarcinoma can also occur[34,35]. Endometrial polyp formation may be dependent on the type and dosage of the estrogen and progestogen. Especially a progestogen with high antiestrogenic activity may play an important preventive role in the development of endometrial polyps[32].

2. Diabetes, hypertension and obesity

Some authors postulate that metabolic anomalies, such as diabetes, hypertension, dyslipidemia and obesity, are independent risk factors for the development of endometrial polyps. Women with BMI≥30 have a higher rate of polyps than other women (52% versus 15%)[36]. A recent study found that insulin resistance plays an important role in the development of benign endometrial pathologies (polyp and/or hyperplasia without atypia). The prevention and the treatment of obesity and diabetes is a key factor in treating recurrent endometrial polyps[37].

3. Dysregulations in the immune system and progesterone deficiency

Recent studies indicate that dysregulations in the immune system participate in the development of a variety of symptoms, such as aging, obesity and hypertension, many of which are risk factors for endometrial polyps. Based on these discoveries, Zhu Y et al. investigated the cellular immune system in premenopausal women with and without endometrial polyps[38]. In women who developed recurrent EP, the $CD4^+$ T cells presented higher preoperative and postoperative RORC, IFN-γ, and IL-17 expression, as well as lower postoperative FOXP3 and TGF-β expression than hysteroscopic polypectomy-treated women without EP recurrence[38]. These data demonstrated an association between $CD4^+$ T cell imbalance and recurrent EP development. Kosei N et al., in their 130 patient-study, found that progesterone deficiency and local immune imbalance with severe hypofunctional NK cells against viral and fungal infections resulted in excessive endometrial cell proliferation and the development of an isolated polyp[39]. Micropolyps, as a macroscopic manifestation of an active inflammatory process in chronic endometritis, are characterized by focal infiltrates of leukocytes (CD45), macrophages (CD68), plasma cells (CD138) and NK (CD56) cells, whose activity leads to excess abnormal proliferation of the endometrium, even in the absence of hormone receptor disorders[39].

4. Other influencing factors

One recent case-control study shows that the prevalence of endometrial polyps is higher in infertile patients with fallopian tube obstruction than in patients with fallopian tube patency[40].

Risk factors for recurrence and recurrence rate

Hysteroscopic resection is a safe and simple procedure which effectively removes polyps, but endometrial polyps can recur. Some studies suggest postoperative recurrence rates of the endometrial polyps to range from 2.5% to 43.6%[41]. Others have suggested recurrence rates of up to 46%, and therefore it is important to identify risk factors associated with recurrence[42].

Gu F et al. compared the incidence of recurrence between a cohort with a high number (≥6) of endometrial polyps and a single-endometrial polyp cohort among reproductive-age patients after polypectomy[43]. The authors concluded that a high number of EP, endometriosis, and previous polypectomy history are independent risk factors for recurrence[43]. The hyperplastic polyp without atypia has a higher risk of postoperative recurrence than that of benign polyps (43.6% vs. 8.3%), although benign polyps have a certain ability to relapse[44,45].

Infertile women are more likely to suffer from endometrial polyps, which suggests a causative relationship between endometrial polyps and infertility. However, it is difficult to explain why some women have a tendency to experience polyp recurrence and others do not. The recurrence of endometrial polyps might be due to the polypoid background in the endometrium, resulting from genetic aberrations. The factors influencing postoperative recurrence potential of benign endometrial polyps have limited data[41,46-48].

One study analyzed 282 women with endometrial polyps in both pre- and postmenopausal period[48]. It shows that after hysteroscopic polypectomy, the recurrence rate of endometrial polyps is 13.3%, and that hyperplastic polyps without atypia recur more frequently than benign ones[48].

Management of recurrent endometrial polyps

The indications of treatment for women with endometrial polyps are: symptomatic endometrial polyps, obesity, infertility, the need to exclude malignancy.

In asymptomatic women, polypectomy is prefferd if: polyp >1.5 cm, multiple polyps, polyp prolapsed through the cervix.

Conservative management

A review of 46 studies, including more than 11.000 women, shows that most polyps are not malignant[49]. The prevalence of atypia and malignancy was 0.8% in premenopausal women and 3.1% in postmenopausal women[49]. This low malignancy rate allows a conservative management.

Metabolic anomalies play an important role in the development of benign endometrial pathologies. The prevention and the treatment of obesity and diabetes are key factors in treating recurrent endometrial polyps[37].

Expectant management with no intervention is an option. Moreover, polyps may spontaneously regress in approximately 25% of cases. Smaller polyps regress more likely than polyps with 10 mm in length. The conservative management of asymptomatic polyps is an option only after the discussion with the patient[30,50].

Medical management

The use of some types of hormonal therapies may have a preventative role for polyp formation.

The use of levonorgestrel-releasing intrauterine device is reported to reduce the incidence of endometrial polyps[46,51]. Wu X et al. studied 250 cases of hysteroscopic resection for endometrial polyps[52]. They found that levonorgestrel intrauterine system may inhibit the recurrence and formation of endometrial polyp by lowering the expressions of estrogen receptor (ER), progesterone receptor (PR) and insulin-like growth factor-1 (IGF-1)[53]. Another study supports the levonorgestrel intrauterine system[53]. The effect of levonorgestrel intrauterine system is superior to that of oral progestin, conclude the authors[53].

A retrospective study aimed to investigate the effects of three cycles of subcutaneous progesterone administered during the luteal phase on the regression rate of symptomatic and asymptomatic endometrial polyps in premenopausal woman[54]. The regression rate of endometrial polyps in women treated with subcutaneous progesterone was compared with the wait-and-see patients. The regression in the number and/or dimensions of the polyps was greater in the treatment group than the control group. The regression rate was 47.5% and 12.5%, respectively ($p<0.001$)[54]. Another study analyzed 98 patients who were confirmed with endometrial polyps and underwent hysteroscopyc polypectomy[55]. The patients were dividend in two groups: one group was treated with progesterone hormone drugs after hysteroscopic operation, and the other group was not treated with progesterone hormone after hysteroscopic operation. The authors conclude that post-hysteroscopic progesterone hormone therapy have favorable clinical effect in treating endometrial polyps, as it can effectively prevent the recurrence of endometrial polyps, restore the level of hemoglobin, and reduce endometrial thickness[55].

GnRHa (gonadotropin-releasing hormone antagonist) can be used before hysteroscopic resection. This option has many side effects and is more expensive than excisional surgery alone. There are no data to support the use of GnRHa in this setting[56].

Hysteroscopic resection

Postmenopausal symptomatic women have a higher risk of premalignant and malignant tissue changes[37] and many studies show that in infertile women hysteroscopic polypectomy improves fertility and increases

pregnancy rates. The removal of endometrial disease by blind curettage is successful in less than 50% of cases, and in many cases the removal is incomplete[57-63]. Hysteroscopic polypectomy is the gold standard regarding the surgical management of endometrial polyps. Hysteroscopy has many advantages: direct vision that allows the complete removal of the polyps while preserving the adjacent endometrium[40]. Moreover, the levonorgestrel intrauterine device is not an option for women who want to conceive. Infertile women should be counseled to achieve a pregnancy in the next couple of months after hysteroscopic polypectomy, and as soon as possible before polyp recurrence[46].

Radical surgical options

Hysterectomy is the only way that proves no endometrial polyp recurrence and guarantees no potential for malignancy. It should be taken in consideration that hysterectomy is a major surgical procedure with potential for morbidity. The patients should be counseled about its risks and implications. There are no comparative data for conservative and radical treatments. When atypical hyperplasia or malignancy is diagnosed by histopathological examination within an endometrial polyp, the woman should be treated in accordance with the guidelines for the treatment of atypical endometrial hyperplasia or endometrial cancer, respectively[46].

Conclusions

Endometrial polyps are a common finding in gynecology, with low malignancy rate progression. The postoperative polyp recurrence might result in the reappearance of abnormal uterine bleeding or infertility. Limited data are available about the factors that influence postoperative recurrence. Some studies show that the number of endometrial polyps and the follow-up duration are major factors that determine the recurrence potential after hysteroscopic polypectomy. A higher number of endometrial polyps and longer follow-up duration are associated with a greater potential of polyp recurrence.

Correcting metabolic anomalies, such as diabetes, hypertension and dyslipidemia, decreases the risk of recurrence. Weight loss also plays an important role in polyps recurrence.

When hysteroscopic treatment is available, blind curettage should not be used as a diagnostic or therapeutic intervention. When an endometrial polyp is diagnosed or suspected and hysteroscopy is not available, the patient should be referred for appropriate treatment.

Progesterone deficiency determines a local immune imbalance. Progestogen with high antiestrogenic activity plays an important preventive role in the recurrence of endometrial polyps. Post-hysteroscopic progesterone hormone therapy has a favorable clinical effect in treating endometrial polyps, as it can effectively prevent the recurrence of endometrial polyps, restore the level of hemoglobin and reduce endometrial thickness.

The levonorgestrel intrauterine device is not an option for women who want to conceive. Infertile women should be counseled to achieve a pregnancy in the next couple of months after hysteroscopic polypectomy, and as soon as possible before polyp recurrence.

When atypical hyperplasia or malignancy is diagnosed by histopathological examination within an endometrial polyp, the woman should be treated in accordance with the guidelines for the treatment of atypical endometrial hyperplasia or endometrial cancer, respectively. ■

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