REVIEW

NEW TIPS DIAGNOSING AND MANAGING ENDOMETRIAL POLYPS

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ABSTRACT

Endometrial polyps (EP) are common lesions that rarely turn malignant. Associated with abnormal uterine bleeding and infertility, the mechanisms of how it affects conception are not yet fully discovered and understood. Diagnosis is now made easy using different imaging techniques. With great sensitivity, we are able to identify and treat polyps using hysteroscopy. Because there is not yet a generally accepted guide of how to treat EP in women looking to conceive, we reviewed recent literature to see if we are closer to finding the best management of infertility cases with endometrial polyps. Recent studies suggest a correlation between removal and high pregnancy rates in natural conception and intrauterine insemination. Still, we do have conflicting results regarding managing endometrial polyps in assisted reproductive techniques.

KEYWORDS: *endometrial polyps, infertility, hysteroscopic removal, adjuvant therapies*

INTRODUCTION

Endometrial polyps (EP) are common lesions representing focal hyperplasia of the basal stratum of the endometrial lining that can occupy a small space or the whole uterine cavity [1]. Usually, benign formations can have multiple locations in the uterine cavity and vary in size [2]. Found in fertile and menopausal women alike, the prevalence of this pathology differs conditional to the studied population between 7.8% and 34.9% [3], [4]. Associated with abnormal uterine bleeding and infertility, EP can also be asymptomatic and be incidentally discovered at a routine check-up, making the true incidence unknown [5]. Nowadays, thanks to modern imaging techniques applied in clinical practice, more cases are discovered, making it seem to increase the incidence rate [6].

Women examined for infertility are often diagnosed with endometrial polyps, which seem to be the most commonly detected uterine structural abnormality (16.7%) in patients with recurrent implantation failures after IVF [7].

EP may cause infertility by preventing successful embryo implantation within the uterus through an intrauterine inflammation process or modified production of endometrial receptivity factors, disrupting the uterine lining, and inhibiting movement of the sperm [8].

RESULTS AND DISCUSSION

Pathogenesis

Many theories have been studied regarding the pathogenesis of the endometrial polyp. A recent systematic review suggests that estrogen-related factors are vital in the onset of polyps. Evidence regarding the existence of a higher concentration of estrogen receptors found in EP compared to a normal epithelium implies estrogen stimulation related to their development, mediating the pro-proliferative effect [9]. Reduced progesterone receptors are thought to make the polyps less responsive to decidualization and menstrual shedding. As a consequence, the persistence of the polyps could increase its susceptibility to mutation and malignant transformation [10].

Estrogen's importance in the etiology of EP is also suggested because they are rarely diagnosed before menarche. Also, studies show that exogenous estrogen as tamoxifen and those used in hormone replacement therapy may be promoters of polyp formation.

Tamoxifen has an anti-estrogenic impact on breast tissue but has estrogenic effects on the uterus, and because of this, it is associated with a high frequency of proliferative lesions: hyperplasia, polyps, and endometrial cancer. The prevalence of EP in women who underwent tamoxifen treatment is between 30-60% [11].

The risk of malignancy increases with age, menopausal status, and the use of tamoxifen [12].

Other factors associated with endometrial polyps are age and obesity, hypertension and diabetes, and some gynecological pathologies like cervical polyps and endometriosis [13], [14].

Chronic inflammation and other molecular mechanisms seem to play a part in the formation of EP. Studies show a higher concentration of Cyclooxygenase-2(COX-2) as well as an increase of endometrial aromatase, elevated B-cell lymphoma 2 protein expression, and mutations in genes such as the HMGIC and HMGI[Y] [15], [16].

Diagnosis

The diagnosis of a polyp is usually made through a 2D Transvaginal ultrasonography (TVUS) performed in the proliferative stage of the endometrium (Figure 1). Other methods are better at detecting EP, such as saline infusion sonography (SIS) (Figure 2) and the golden standard in diagnosis and treatment-hysteroscopy (Figure 3), (Figure 4).

As a daily practice, we use 2D TVUS for the detection of suggestive hyperechogenic masses best performed during the early proliferative phase where the endometrium is thin. A thick endometrium makes diagnosis hard especially distinguishing between a true polyp and a polypoid endometrium.

In a prospective 5-year study of 793 women, the detection rate of intrauterine abnormalities using transvaginal ultrasonography had a 96% sensitivity and 86% specificity, making the authors suggest this modality as a first investigation [17].

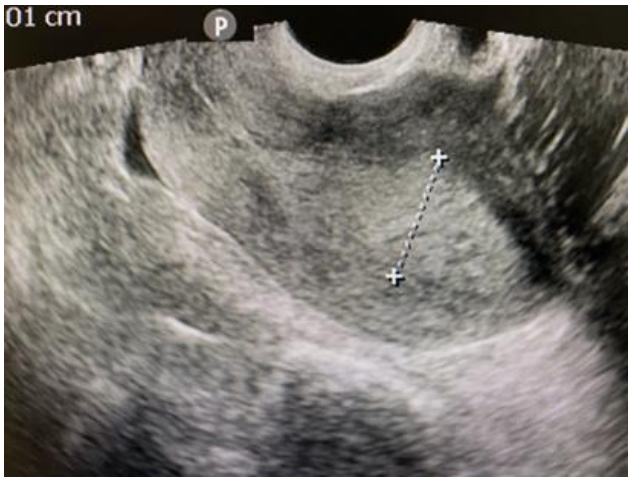

Figure 1 – Endometrial polyp seen at the2D TVUS (Prof. Dr. Claudia Mehedințu's collection)

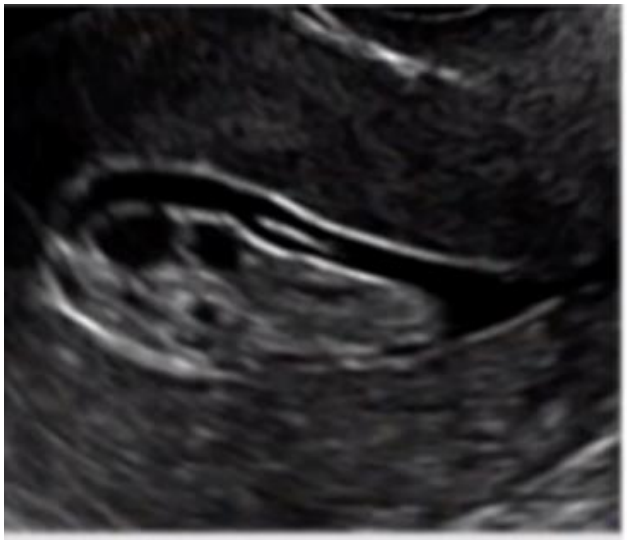

Figure 2 – Endometrial polyp seen at the saline infusion sonography (Prof. Dr. Claudia Mehedințu's collection)

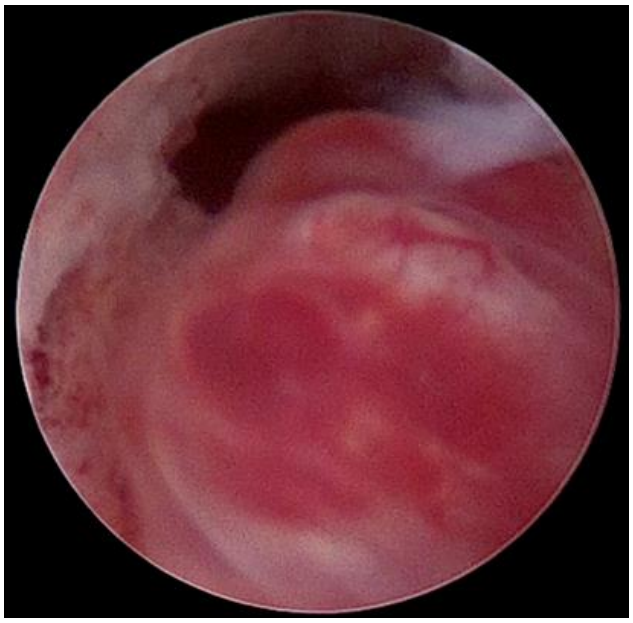

Figure 3 – Endometrial polyp seen on the posterior wall of the uterus, at hysteroscopy (Prof. Dr. Claudia Mehedințu's collection)

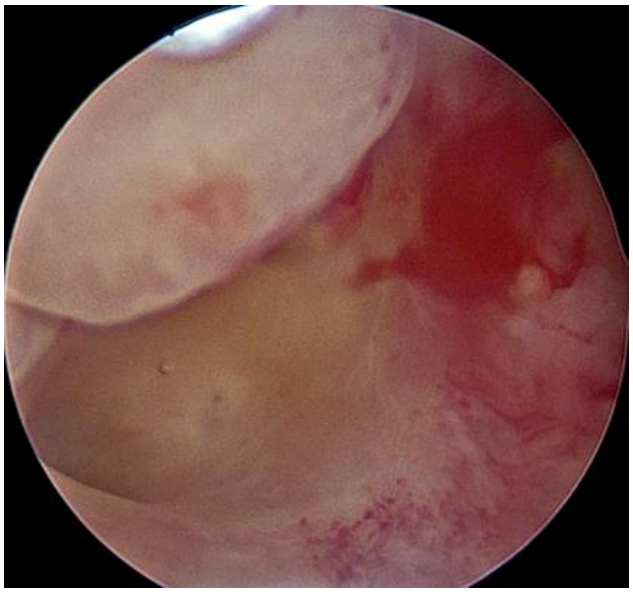

Figure 4 – Endometrial polyp seen on the anterior wall of the uterus, at hysteroscopy (Prof. Dr. Claudia Mehedințu's collection)

Adding color flow Doppler can allow visualization of the single vessel feeding the endometrial polyp, increasing overall detection rates [18].

SIS is a maneuver in which saline fluid is injected into the uterine cavity through the cervix for better visualization during TVUS examination. Saline infusion sonography has a superior detection rate when compared to 2DTVUS. A systematic review and meta-analysis have been found to be highly accurate for all uterine abnormalities [19]. The drawbacks are a longer learning curve for the examiner and discomfort for the patient produced by fluid instillation in the cavity and leakage [20].

The golden standard in diagnosing endometrial polyps is considered hysteroscopy. It allows the practitioner to diagnose and treat all during the same intervention.

Management

Expectant management is considered an option for premenopausal women with small size EP (<10 mm), with a 25% rate of cases that spontaneous regress [21].

Medical management is not considered a viable first option treatment, with Gonadotropin-releasing hormone agonists being studied as an adjuvant for surgical removal.

Of many drugs proposed to adjoin surgical intervention, only danazol and GnRH analogs have studies that back up their efficacy [22].

In a prospective randomized study comparing the two types of drugs administrated before hysteroscopy for different uterine pathologies, including endometrial polyps, they draw the conclusion that both treatments reduce endometrial thickness, intraoperative bleeding, and difficulties and duration of surgery. With a shorter operative time, less infusion liquid is used, meaning a lower risk of absorption and electrolytic imbalances. [23].

The downside is the cost of these drugs and preoperative treatment duration, which refrain us from prescribing for minor hysteroscopic interventions.

Another medical treatment proposed is progesterone therapy, either oral or levonorgestrel-impregnated intrauterine device. The focus of recent studies was to find out if they can replace surgical treatment.

Although levonorgestrel intrauterine devices have been found to have a better success rate than oral progesterone in reducing endometrial hyperplasia, few studies suggest that it can prevent endometrial polyps in patients under tamoxifen treatment and reduce the occurrence of polyps in women independent of tamoxifen treatment [24], [25]. Further evidence is necessary to draw a conclusion.

Progesterone treatment is not used as an alternative treatment for hysteroscopy in endometrial polyps but as an adjuvant.

Hysteroscopic polypectomy remains the golden standard with different systems of removal as a monopolar loop, the most frequently used, microscissors, or graspers and hysteroscopic morcellator. In the absence of equipment, blind curettage can be performed but with lower success rates.

Recurrence is a problem with simple surgical treatment. Studies show a recurrence rate high as 45.5% when hysteroscopic polypectomy is performed alone [26], [27], [28].

Recent findings suggest diverse methods of recurrence prevention such as oral progesterone preparations, short-action contraceptives, gestrinone, GnRH, and levonorgestrel intrauterine devices. In a 2018 study, Fangfang Li et al. [29] evaluated the outcome of 98 patients that underwent hysteroscopy for endometrial polyp followed by four months course of treatment with oral progesterone. They concluded that the recurrence quota was lower than the control group only treated with hysteroscopic polypectomy 2.04% vs 12.24% [29].

Short action contraceptives have been shown to control the growth of the endometrium and also to decrease the risk of endometrial polyps. The response of polyps to oral contraceptives depends on the shape of the polyp. Sessile polyps have a higher regression rate than pedunculated polyps under oral contraceptive treatment [30].

A personalized treatment course is proposed depending on the age and risk factors. The first approach is hysteroscopic polypectomy associated with GnRH agonist (Difereline) for the first six months and progestin as a second stage treatment. In women of reproductive age, polypectomy and oral progesterone were administered after. It shows promising results with a low recurrence rate. Personalized treatment is also cost-effective and reduces radical interventions [31].

Impact on fertility

The impact on fertility is still difficult to pinpoint as the mechanisms are still not eluded; endometrial polyps may affect fertility in many ways. The first way could be a mechanical interference, depending on the position of the polyp, it can block sperm transport if it is located in the cervical ostium or the opening of the fallopian tube [32].

A retrospective study conducted by Yanaihara et al. [33] regarding 260 women that underwent polypectomy concludes a correlation between the location of the polyps and pregnancy rates. The results of pregnancy rates within six months postintervention were 57.4% for EP positioned at the utero-tubal junction, 40.3% for multiple endometrial polyps, 28.5% were posterior wall polyps, 18.8% for lateral wall polyps, and anterior uterine wall EP, a percentage of 14.8% [33].

The size of the EP may have a mechanical effect. Occupying a larger space in the uterine cavity may block the embryo's implantation acting as an intrauterine device and, as such, can generate an inflammatory response comparable to the effect found in women carrying IUDs. Although, studies have not yet reached a consensus regarding how size affects fertility.

Another way to affect infertility is through its biochemical effects. Compared to normal endometrium, EP have elevated levels of matrix metalloproteinases (MMPS), cytokines, and glycodelin, impacting implantation and blocking sperm-oocyte interaction.

Glycodelin is a glycoprotein put in the spotlight by studies in recent years for its implication in the process of implantation and angiogenesis [34]. It has been found in high concentration in endometrial polyps affecting fertility by elevating progesterone levels in the follicular and the peri-ovulatory period impairing fertilization and implantation [34].

An immune suppressor with the role of helping the patient's body to accept the allogenic embryo is placenta protein 14. It has been found to be in lower quantity in EP when compared to a normal endometrium [2].

In a case-control study, BW. Rackow et al. demonstrated a relevant decrease in HOXA10 and HOXA11, markers of endometrial receptivity, thus an association with low pregnancy rates in women with endometrial polyps through impairment of endometrial receptivity [35].

Management in fertility

In terms of natural conception, observational studies using the Cochrane database suggest a 63% pregnancy rate after

simple hysteroscopic polypectomy for women with no other cause of infertility [36].

When comparing pregnancy rates in a retrospective study on infertile women, pregnancy rates were higher after polypectomy (78.3%) than for women with a normal uterine cavity (41.2%) [37].

Shokeir et al. and Spiewankiewicz et al. reported high pregnancy rates, 50-76% for women who underwent polypectomy within 12 months [38], [39].

Intrauterine insemination

More evidence is gathering that polypectomy before intrauterine insemination (IUI) improves pregnancy rates compared to expectation management. When compared, the pregnancy rate in the groups of women that underwent polypectomy is significantly higher than the control group with either polyp biopsy or no treatment, rates as high as 63% vs. 28.2% were reported [40], [41], [42]. In another prospective study, spontaneous pregnancy was noted in the 3-month waiting period before IUI, suggesting the impact on fertility a polyp can have [43].

Management is not yet precise when discussing in vitro fertilization (IVF) if an endometrial polyp is discovered during the evaluation. It can include the option of continuing ovarian stimulation and fresh embryo transfer or polypectomy with freezing all embryos and transferring them in a subsequent cycle or simply removing polyp with treatment cancellation.

Lass et al. [44] studied the effects of polypectomy on 83 patients divided into two groups. The first was completed with standard embryo transfer treatment, and the second group underwent hysteroscopy after oocyte retrieval and later transfer of frozen embryos with no significant difference in clinical pregnancy rates between the two [44]. Other randomized studies seem to have similar results, with Ghaffari et al. reporting no significant differences in the result of IVF between patients who underwent polypectomy and those who did not [45]. The same observation was made when it comes to polypectomy before intracytoplasmic sperm injection (ICSI) versus the control group that did not have the intervention. Tiras et al. even proposed that when discovering endometrial polyps smaller than 1,5 cm during stimulation, removing or canceling embryo transfer is unnecessary [46].

Yang et al. [47] demonstrated different results when comparing hysteroscopic polypectomy during ovarian stimulation with a later transfer of vitrified warmed embryos with a control group receiving fresh embryo transfers. The pregnancy rates did differ in favor of the first group with a 63% versus 42% [47].

Although, comparing results from a group that received fresh embryos and another receiving vitrified warmed embryos may limit the ability to assess the impact of hysteroscopic polypectomy on IVF outcomes correctly.

A 2021 review of studies involving the management of EP in infertile women concludes that it is best to remove an endometrial polyp in women with unexplained infertility [48]. However, more information is resurfacing that in some cases, an EP smaller than 10 mm could regress spontaneously in a 2-3-month period and would not need hysteroscopic removal [49].

CONCLUSION

Although endometrial polyps are a common diagnostic, especially in women with no other apparent cause of infertility, we still don't know precisely the mechanisms behind impairing conception. Nowadays, diagnosing a polyp is easily done through many imaging techniques, and hysteroscopy remains the golden standard in detection in treatment. Personalized treatment should be considered, especially for women seeking to conceive. We have some evidence that removing polyp could increase pregnancy rates in spontaneous conception and IUI, but much remains unknown when studying assisted reproductive techniques. More studies are necessary to draw conclusions about the best management in endometrial polyps.

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