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These experts discuss the factors that incur increased risk for malignant endometrial polyps, the relationship between chronic endometritis and endometrial polyps, whether the etonogestrel subdermal implant can treat EIN, and new endometrial ablation technology

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Keeping current with causes of and treatments for abnormal uterine bleeding (AUB) is important. AUB can have a major impact on women's lives in terms of health care expenses, productivity, and quality of life. The focus of this Update is on information that has been published over the past year that is helpful for clinicians who counsel and treat women with AUB. First, we focus on new data on endometrial polyps, which are a common cause of AUB. For the first time, a

meta-analysis has examined polyp-associated cancer risk. In addition, does a causal relationship exist between endometrial polyps and chronic endometritis? We also address the first published report of successful treatment of endometrial intraepithelial neoplasia (EIN, formerly complex endometrial hyperplasia with atypia) using the etonogestrel subdermal implant. Last, we discuss efficacy data for a new device for endometrial ablation, which has new features to consider.

What is the risk of malignancy with endometrial polyps?

Sasaki LM, Andrade KR, Figueiredo AC, et al. Factors associated with malignancy in hysteroscopically resected endometrial polyps: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2018;25:777-785.

In the past year, 2 studies have contributed to our understanding of endometrial polyps, with one published as



WHAT THIS EVIDENCE MEANS FOR PRACTICE

The study takeaways regarding clinical and demographic risk factors suggest that menopausal status, age greater than 60 years, the presence of AUB, diabetes, hypertension, obesity, and tamoxifen use have an increased risk for premalignant and malignant lesions.

This study is important because its findings will better enable physicians to inform and counsel patients about the risks for malignancy associated with endometrial polyps, which will better foster discussion and joint decision-making about whether or not surgery should be performed.

the first ever meta-analysis on polyp risk of malignancy.

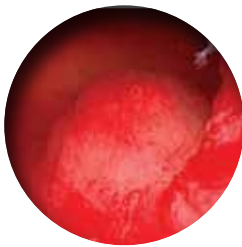
What can information from more than 21,000 patients with polyps teach us about the risk factors associated with endometrial malignancy? For instance, with concern over balancing health care costs with potential surgical risks, should all patients with endometrial polyps undergo routine surgical removal, or should we stratify risks and offer surgery to only selected patients? This is the first meta-analysis to evaluate the risk fac-

tors for endometrial cancer (such as obesity, parity, tamoxifen use, and hormonal therapy use) in patients with endometrial polyps.

Risk factors for and prevalence of malignancy

Sasaki and colleagues found that about 3 of every 100 patients with recognized polyps will harbor a premalignant or malignant lesion (3.4%; 716 of 21,057 patients). The identified risk factors for a cancerous polyp included: menopausal status, age greater than 60 years, presence of AUB, diabetes mellitus, hypertension, obesity, and tamoxifen use. The risk for cancer was 2-fold greater in women older than 60 years compared with those younger than age 60 (prevalence ratio, 2.41). The authors found no risk association with use of combination hormone therapy, parity, breast cancer, or polyp size.

The investigators advised caution with using their conclusions, as there was high heterogeneity for some of the factors studied (including age, AUB, parity, and hypertension).



New evidence associates endometrial polyps with chronic endometritis

Cicinelli E, Bettocchi S, de Ziegler D, et al.

Chronic endometritis, a common disease hidden behind endometrial polyps in premenopausal women: first evidence from a case-control study. J Minim Invasive Gynecol. 2019. S1553-4550(19)30056-1. doi: 10.1016/j.jmig.2019.01.012.

The second important study published this year on polyps was conducted by Cicinelli and colleagues and suggests that inflammation may be part of the pathophysiology behind the common problem of polyps. The authors cite a recent study that showed that abnormal expression of “local” paracrine inflammatory mediators, such as

interferon-gamma, may enhance the proliferation of endometrial mucosa.¹ Building on this possibility further, they hypothesized that chronic endometrial inflammation may affect the pathogenesis of endometrial polyps.

Details of the study

To investigate the possible correlation between polyps and chronic endometritis, Cicinelli and colleagues compared the endometrial biopsies of 240 women with AUB and hysteroscopically and histologically diagnosed endometrial polyps with 240 women with AUB and no polyp seen on hysteroscopy.

The tissue samples were evaluated with immunohistochemistry for CD-138 for plasma cell identification.

The study authors found a significantly higher prevalence of chronic endometritis in the group with endometrial polyps than in the group without polyps (61.7% vs 24.2%, respectively; $P < .0001$). They suggest that this evidence supports the hypothesis that endometrial polyps may be a result of endometrial proliferation and vasculopathy triggered by chronic endometritis.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The significance of this study is that there is a possible causal relationship between endometrial polyps and chronic endometritis, which may expand the options for endometrial polyp therapy beyond surgical management in the future.

Can endometrial intraepithelial neoplasia be treated with the etonogestrel subdermal implant?



Wong S, Naresh A. Etonogestrel subdermal implant-associated regression of endometrial intraepithelial neoplasia. *Obstet Gynecol.* 2019;133:780-782.

Recently, Wong and Naresh gave us the first case report of successful treatment of EIN using the etonogestrel subdermal implant. With so many other options available to treat EIN, some of which have been studied extensively, why should we take note of this study? First, the authors point out the risk of endometrial cancer development among patients with EIN, and they acknowledge the standard recommendation of hysterectomy in women with EIN who have finished childbearing and are appropriate candidates for a surgical approach. There is also concern about lower serum etonogestrel levels in obese patients. In this case, the patient (aged 36 with obesity) had been nonadherent with oral progestin therapy and stated that she would not adhere to daily oral therapy. She also declined hysterectomy, levonorgestrel-releasing intrauterine device therapy, and injectable progestin

therapy after being counseled about the risk of malignancy development. She consented to subdermal etonogestrel as an alternative to no therapy.

EIN regressed. Endometrial biopsies at 4 and 8 months showed regression of EIN, and at 16 months after implantation (as well as a dilation and curettage at 9 months) demonstrated an inactive endometrium with no sign of hyperplasia.

FAST TRACK

Although not appropriate for first-line therapy, the etonogestrel subdermal implant may be a reasonable option to manage EIN

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The authors remain cautious about recommending the etonogestrel subdermal implant as a first-line therapy for EIN, but the implant was reported to be effective in this case that involved a patient with obesity. In cases in which surgery or other medical options for EIN are not feasible, the etonogestrel subdermal implant is reasonable to consider. Its routine use for EIN management warrants future study.

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New endometrial ablation technology shows promising benefits

Levie MD, Chudnoff SG. A prospective, multicenter, pivotal trial to evaluate the safety and effectiveness of the AEGEA vapor endometrial ablation system. J Minim Invasive Gynecol. 2019;26:679-687.

Do we need another endometrial ablation device? Are there improvements that can be made to our existing technology? There already are several endometrial ablation devices, using varying technology, that currently are approved by the US Food and Drug Administration (FDA) for treatment of AUB. The devices use bipolar radiofrequency, cryotherapy, circulating hot fluid, and combined thermal and radiofrequency modalities. Additional devices, employing heated balloon and microwaves, are no longer used. Data on a new device, approved by the FDA in 2017 (the AEGEA Vapor System, called Mara), were recently published.

Details of the study

Levie and colleagues conducted a prospective pivotal trial on Mara's safety and effectiveness. The benefits presented by the authors

include that the device 1) does not require that an intrauterine array be deployed up to and abutting the fundus and cornu, 2) does not necessitate cervical dilatation, 3) is a free-flowing vapor system that can navigate differences in uterine contour and sizes (up to 12 cm in length), and 4) accomplishes ablation in 2 minutes. So there are indeed some novel features of this device.

This pivotal study was a multicenter trial using objective performance criterion (OPC), which is based on using the average success rates across the 5 FDA-approved ablation devices as historic controls. In the study an OPC of 66% correlated to the lower bound of the 95% confidence intervals. The primary outcome of the study was effectiveness in the reduction of blood loss using a pictorial blood loss assessment score (PBLAS) of less than 75. Of note, a PBLAS of 150 was a study entry criterion. FIGO types 2 through 6 fibroids were included in the trial. Secondary endpoints were quality of life and patient satisfaction as assessed by the Menorrhagia Impact Questionnaire and the Aberdeen Menorrhagia Severity Score, as well as the need to intervene medically or surgically to treat AUB in the first 12 months after ablation.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The takeaway is that the AEGEA device appears to be effective for endometrial ablation and offers the novel features of not relying on an intrauterine array to be deployed up to and abutting the fundus and cornu, not necessitating cervical dilatation in all cases, and offering a free-flowing vapor system that can navigate differences in uterine contour and sizes quickly (approximately 2 minutes).

The fact that new devices for endometrial ablation are still being developed is encouraging, and it suggests that endometrial ablation technology can be improved. Although AEGEA's Mara system is not yet commercially available, it is anticipated that it will be available at the start of 2020. The ability to treat large uteri (up to 12-cm cavities) with FIGO type 2 to 6 fibroids with less cervical dilatation makes the device attractive and perhaps well suited for office use.

Efficacy, satisfaction, and quality of life results

At 12 months, the primary effectiveness endpoint was achieved in 78.7% of study participants. The satisfaction rate was 90.8% (satisfied or very satisfied), and 99% of participants showed improvement in quality of life scores. There were no reported serious adverse events. ●

Reference

1. Mollo A, Stile A, Alviggi C, et al. Endometrial polyps in infertile patients: do high concentrations of interferon-gamma play a role? *Fertil Steril*. 2011;96:1209-1212.