An Update on the Management of Endometrial Hyperplasia

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Endometrial hyperplasia is known to be a precursor lesion for development of endometrial adenocarcinoma, which is the most common gynaecological cancer in Hong Kong. Recently, the Royal College of Obstetricians and Gynaecologists/British Society for Gynaecological Endoscopy (RCOG/BSGE) published a joint guideline in February 2016 on the management of endometrial hyperplasia. In this article, we review the development of the classification of endometrial hyperplasia, as well as the investigation and management of endometrial hyperplasia in reference both to the Hong Kong College of Obstetricians and Gynaecologists and RCOG/BSGE guidelines.
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Introduction

Endometrial cancer is the most common gynaecological malignancy in Caucasians and locally in Hong Kong. It ranks fourth among the most common cancers in Hong Kong females[1]. Endometrial hyperplasia is known to be a precursor lesion for endometrial adenocarcinoma. It is defined as irregular proliferation of the endometrial glands with an increase in the gland-to-stroma ratio when compared with proliferative endometrium[2].

In this article, we review the investigation and management of endometrial hyperplasia with reference to the recent Hong Kong College of Obstetricians and Gynaecologists (HKCOG) guidelines[3] published in September 2015 and the Royal College of Obstetricians and Gynaecologists/British Society for Gynaecological Endoscopy (RCOG/BSGE) joint guideline[4] published in February 2016.

Classification

Previously, the most widely adopted classification for endometrial hyperplasia was the World Health Organization (WHO) 1994 classification system[5], in which endometrial hyperplasia was classified into four categories based on the glandular architectural complexity and nuclear atypia: (i) simple hyperplasia, with 1% risk of progression to endometrial cancer; (ii) complex hyperplasia, with 3% risk of progression to endometrial cancer; (iii) simple hyperplasia with atypia; and (iv) complex hyperplasia with atypia. The last two have a higher risk of progression to endometrial cancer of 8% and 29%, respectively[6]. Among complex hyperplasia with atypia, a 50% risk of concomitant cancer has been reported[7].

In 2000, the Endometrial Collaborative Group redefined the terminology. Endometrial precancers were collectively designated endometrial intraepithelial neoplasia (EIN) in recognition of their monoclonal growth. This also avoids confusion with a benign hormonal effect[8]. Long-term follow-up study of women with endometrial hyperplasia suggested that the EIN classification has higher accuracy to predict the development of future malignancies than the WHO 1994 classification[9], but the system is not extensively used in the UK or locally in Hong Kong.

The WHO 2003 classification defines EIN as a 'histological presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric and clinical outcome data', with only 79% of atypical hyperplasia translating to EIN[7]. In the latest WHO classification published in 2014, endometrial hyperplasia is simply divided into two categories: (i) hyperplasia without atypia and (ii) atypical hyperplasia. Atypical hyperplasia exhibits mutations that are typical of invasive endometrial cancer, and these changes are not evident in hyperplasia without atypia. The 2014

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classification system not only allows interchangeable diagnosis between EIN and atypical hyperplasia, it also reflects a new understanding of molecular genetic changes[10].

Methods of Diagnosis

Histological examination of endometrial tissue is necessary to diagnose endometrial hyperplasia. Outpatient endometrial sampling is convenient and has a high overall accuracy for diagnosing endometrial cancer. The RCOG/BSGE guidelines[4] suggest diagnostic hysteroscopy when outpatient endometrial sampling fails or is non-diagnostic, or when endometrial hyperplasia is diagnosed within a polyp or other discrete focal lesion. The HKCOG guidelines[3] suggest diagnostic hysteroscopy with targeted biopsy or dilatation and curettage, when endometrial hyperplasia is diagnosed on endometrial biopsy, in order to exclude carcinoma or atypical endometrial hyperplasia before commencement of treatment.

In a meta-analysis of accuracy of endometrial sampling, the sensitivity for detecting cancer in postmenopausal and premenopausal women using pipelle was 99.6% and 91%, respectively. For atypical hyperplasia, the sensitivity was 81%[11]. The diagnostic accuracy of hysteroscopy alone for hyperplasia is only modest when compared with that of cancer[12], therefore targeted biopsy or dilatation and curettage should be performed with diagnostic hysteroscopy to improve the diagnostic accuracy.

With regard to imaging, transvaginal ultrasound may play a role in diagnosis. It helps to detect any endometrial polyp or focal lesion by assessing the regularity of the endometrial lining. For diagnosis of endometrial hyperplasia, it should be performed in conjunction with endometrial biopsy for histological examination. Computed tomographic scan and magnetic resonance imaging (MRI) are not routinely recommended.

Treatment and Surveillance

An algorithm for the management of endometrial hyperplasia is illustrated in the Figure.

Endometrial Hyperplasia without Atypia

The cumulative 20-year progression risk among women with endometrial hyperplasia without atypia is less than 5%. Most cases will regress[13]. Women should be informed that treatment with progestogen has a higher regression rate than observation alone. The regression rate ranges from 74.2% to 81%[6,14] for observation alone compared with 89% to 96% for progestogen treatment[15]. Importantly, reversible risk factors, such as obesity and hormone replacement therapy (HRT), should be identified and corrected if possible.

The first-line progestogen treatment is insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS) that can achieve a higher local concentration and higher regression rate, with less systemic side-effects. Patients are also less likely to require hysterectomy[16]. In addition, LNG-IUS provides effective contraception. The minimal treatment duration is 6 months for regression of disease, although in women with endometrial hyperplasia without atypia up to 5 years is preferable provided any adverse effects are tolerable[4].

An alternative for women who decline LNG-IUS is oral continuous progestogens. The suggested effective regimens include medroxyprogesterone 10 to 20 mg/day, norethisterone 10 to 15 mg/day, and megestrol 160 to 320 mg/day[3]. Similarly, the minimal treatment duration is 6 months. If endometrial hyperplasia persists despite 6 months of treatment with oral continuous progestogens, LNG-IUS should be offered. Cyclical progestogens have been shown to be less effective in inducing regression of endometrial hyperplasia compared with the continuous regimen[17]. Observation or other treatments such as endometrial ablation, combined pills, and gonadotrophin-releasing hormone agonists are not routinely recommended. In view of the high regression rate with progestogen, hysterectomy is not offered as the first-line treatment. It is only indicated in those who show no regression after 12 months of treatment, who progress to atypical hyperplasia, relapse after treatment completion, or have persistent abnormal bleeding, and those who decline to comply with treatment and surveillance.

According to the RCOG/BSGE guidelines[4], endometrial surveillance for endometrial hyperplasia without atypia should be performed every 6 months. In low-risk women, at least two consecutive negative endometrial biopsies are needed prior to discharge. In women at higher risk of relapse such as those with body mass index of ≥ 35 kg/m^2 or those who are treated with oral progestogens, long-term follow-up with annual endometrial sampling is required after two consecutive negative endometrial biopsies. The HKCOG guidelines[3] recommend endometrial sampling every 6 months for 2 years after completion of treatment. Women can be discharged if regression is achieved. Women should be advised about the risks of late recurrence and to seek medical attention if abnormal bleeding occurs.

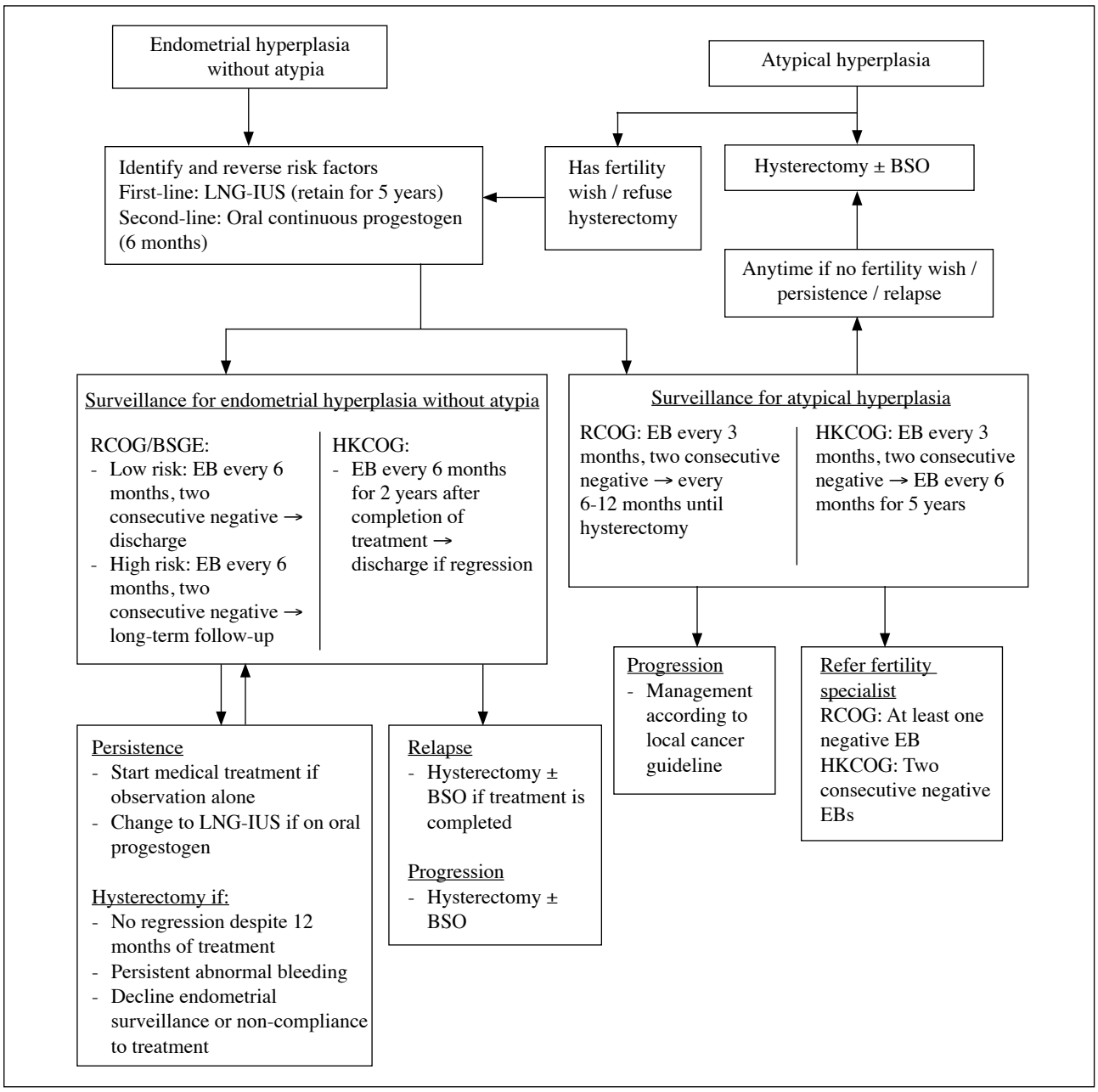

Figure. Algorithm for the management of endometrial hyperplasia

Abbreviations: BSO = bilateral salpingo-oophorectomy; EB = endometrial biopsy; HKCOG = Hong Kong College of Obstetricians and Gynaecologists; LNG-IUS = levonorgestrel-releasing intrauterine system; RCOG/BSGE = Royal College of Obstetricians and Gynaecologists//British Society for Gynaecological Endoscopy

Atypical Hyperplasia

The risk of progression to malignancy is 30% with a risk of concomitant cancer (40-50%) for atypical hyperplasia[6,7]. Thus, total hysterectomy is offered as the first-line treatment. If hysterectomy is to be performed in postmenopausal women, total hysterectomy with bilateral salpingo-oophorectomy is recommended, whereas for premenopausal women, total hysterectomy with bilateral salpingectomy is recommended. The decision to perform bilateral salpingo-oophorectomy should be taken on an individual basis.

Women who wish to retain their fertility or refuse hysterectomy should be counselled about the risks of concomitant endometrial cancer and progression to endometrial cancer, the importance of endometrial surveillance and to delay conception until disease regression. The first-line fertility-sparing treatment is LNG-IUS, and the second-line treatment is oral continuous progestogens. Underlying endometrial cancer should be excluded by hysteroscopy with targeted biopsy or dilatation and curettage. Investigations such as transvaginal ultrasound scan help to exclude ovarian lesions. Tumour

markers (such as CA125) and MRI scan can be considered if clinically indicated.

According to the RCOG/BSGE guidelines[4], endometrial surveillance for women undergoing fertility-sparing treatment should be performed every 3 months. Hysteroscopy with targeted biopsy or dilatation and curettage can be considered as the endometrial sampling method. After two consecutive negative endometrial biopsies, endometrial surveillance every 6 to 12 months should be arranged until hysterectomy is performed. Endometrial sampling can be considered in low-risk women without persistent abnormal uterine bleeding. The HKCOG guidelines[3] advocate endometrial surveillance every 3 months. After two consecutive negative endometrial biopsies, endometrial surveillance can be performed every 6 months for 5 years.

Women who wish to conceive can be referred to a fertility specialist after at least one negative endometrial sample according to the RCOG guidelines, or after two consecutive negative endometrial biopsies according to the HKCOG guidelines[3]. The rationale is that regression of disease is associated with higher implantation and clinical pregnancy rates.

Endometrial Hyperplasia in Special Groups of Women

Women on Hormone Replacement Therapy

It is generally agreed that oestrogen-only HRT should not be used in women with an intact uterus. The indication for HRT should be reviewed carefully. Women with endometrial hyperplasia who wish to continue HRT should be advised to have continuous progestogen, such as LNG-IUS or a continuous combined HRT preparation.

Women on Tamoxifen

Women should be informed about the risks of endometrial hyperplasia and cancer with the use of tamoxifen, but not those taking aromatase inhibitors (e.g. anastrozole, exemestane, and letrozole). Although there is evidence that prophylactic insertion of LNG-IUS can decrease both the formation of endometrial polyps and endometrial hyperplasia[18], its routine use cannot be recommended because of the uncertain risk of breast cancer recurrence.

Women with a History of Hyperplasia Managed according to the Old Classification System

Under the old 1994 WHO classification of endometrial hyperplasia[5], among women with simple hyperplasia without atypia who had a very low risk of disease progression (1%), some were prescribed routine treatment according to their menstrual symptoms. With reference to the new classification system and updated guidelines, treatment with progestogens and endometrial surveillance is required for this group of women. They should be well informed and counselled about the recent evidence and treatment recommendations.

Conclusion

Endometrial hyperplasia is a precancerous lesion that is not uncommon. We should be updated in the classification system and the recommendations in management. The diagnosis can be confirmed by endometrial sampling, or more accurately, by hysteroscopy with targeted biopsy or dilatation and curettage. The first-line treatment of hyperplasia without atypia is insertion of LNG-IUS, and that of atypical hyperplasia is hysterectomy with or without bilateral salpingo-oophorectomy if no fertility wish. In special cases such as those with atypical hyperplasia with fertility wish and those with progression to malignancy, referral to subspecialist care is suggested.

Declaration

All authors have disclosed no conflicts of interest.

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