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TOPIC HIGHLIGHT

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Fertility sparing management of endometrial complex hyperplasia and endometrial carcinoma

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Abstract

The standard treatment of endometrial cancer or atypical hyperplasia is surgical removal of the uterus and ovaries. In early stage disease this has an excellent chance of cure but results in infertility. Although the majority of patients are postmenopausal an increasing number of patients with atypical hyperplasia or endometrial cancer are presenting with a desire to retain their fertile potential. In the last 8 years a number of studies have been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby. Although concerns exist about the risks of medical treatment, those that fail this treatment do not appear to have a significantly poorer prognosis although 20 patients (3.6%) had either ovarian cancer or metastatic disease discovered during treatment or follow up.

Key words: Endometrial cancer; Fertility sparing

Core tip: Early endometrial cancer is successfully treated with hysterectomy in most cases but an increasing number of women develop the disease whilst still hoping to conceive. We are gathering an increasing amount of data to accurately describe the risk they are taking by undergoing medical treatment with progestagens as an alternative.

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INTRODUCTION

Endometrial cancer is the commonest gynaecological malignancy in the western world and usually affects post menopausal women. However up to 14% of these cancers are now diagnosed in the premenopausal with about 4% occurring in those under the age of 40 years in the United States[1]. As the trend to delay childbearing continues a greater number of women are being diagnosed with endometrial cancer at a stage in life when they wish to conceive. Therefore the standard management of hysterectomy with removal of ovaries needs to be fully justified and the possibility of managing patients medically whilst preserving their fertility should be considered. In the last decade a significant number of studies have been published allowing us to assess the success of this medical treatment so that we can advise our patients on the risks of fertility preservation in early stage endometrial cancer. However there are pitfalls of which every gynaecological oncologist should make themselves aware.

DIAGNOSIS

Irregular menstrual bleeding at any age needs to be in-

vestigated and the diagnosis of endometrial carcinoma is made by biopsy from the endometrial cavity either at hysteroscopy or outpatient endometrial sampling. The most accurate assessment is from biopsy obtained at hysteroscopy[2] but even then it can be difficult to make the distinction between atypical hyperplasia (AH) and invasive endometrial carcinoma (EC). As EC is actually found in the hysterectomy when the preoperative diagnosis was thought to be AH in approximately 30% of cases the treatment of both AH and early stage EC should be very similar[3,4].

STAGING

A number of studies have looked at the stage of disease in younger women with endometrial cancer and although the majority are stage 1a grade 1 disease, approximately 20% are found to have disease outside the uterus[5]. In addition up to 25% of women have either synchronous or metastatic ovarian tumours[6]. With standard management of hysterectomy and bilateral salpingo-oophorectomy the extent of disease can be assessed histopathologically and this is how the FIGO staging is determined. However if medical treatment is proposed the major initial disadvantage is the lack of histological confirmation of staging and the reliance on pre treatment imaging.

Ultrasound, computed tomography (CT) and contrast enhanced magnetic resonance imaging (MRI) have been used to stage early endometrial cancers and the MRI is the most accurate being able to predict myometrial invasion with a specificity of 96% and cervical invasion in 88%[7,8].

HORMONAL TREATMENTS

The majority of grade 1 endometrial cancers have progressed from hyperplasia and are thought to have arisen because of hormonal imbalances. Obesity where there is a higher level of circulating oestrogens from fat degradation, and polycystic ovaries where infrequent, anovulatory cycles are a feature suggest that a lack of balanced progesterone is responsible. Various types and doses of progesterones have been used to reverse the hyperplasia and EC. Initially Kinkel *et al*[9] described resolution of an endometrial malignancy in 25% of patients undergoing hysterectomy after treatment with progesterones. Although small doses of progesterone may be sufficient to balance the oestrogen in hormone replacement therapy a much higher does is required in AH and EC in these premenopausal women.

The majority of studies have used Medroxyprogesterone acetate in doses of 400-800 mg daily. This can, if necessary, be taken in divided doses. The next most common is megestrol but a recent study of 148 patients showed patients treated with megestrol had a higher chance of recurrence[10]. The levonorgestrol containing intrauterine device (IUS) has not been successfully when used in isolation. It may be useful for maintenance therapy after remission has been established and a randomised study has just opened in South Korea to evaluate this[11].

A meta analysis has been published involving 403 patients with endometrial cancer and 151 patients with Atypical hyperplasia treated with high dose progestagens[12]. The response rate is 76.2% and 85.6% respectively with endometrial cancer having a recurrence rate of 40.6%. There is a 26% recurrence rate in atypical hyperplasia. Overall 26.3% of those wishing to conceive had a live baby.

In comparison removal of the uterus and ovaries would be expected to give a disease free 5 year survival of 98.2%[13]. A recent review of 148 patients in eight hospitals in South Korea obtained similar response and recurrence free response rates (77.7% and 54% respectively). Of 33 patients who failed to respond to initial treatment, and had a hysterectomy, none of them recurred implying the risk of trying and failing medical treatment is low. Risk factors that increased the risk of recurrence were obesity (body mass index > 25) and a lack of pregnancy[10]. There were no reported deaths from disease in this study but in the meta analysis by Gallos *et al*[1] there were 2 deaths and 20 patients (3.6%) had disease in the ovaries either as a concommitent ovarian tumour or metastasis.

Therefore, despite the risk that more advanced or metastatic disease can be under diagnosed and despite the risk that the EC recurs in a large number of patients there do not appear to be significant long term risks to trying medical treatment.

FOLLOW UP

The various studies have given medical therapy for variable lengths of time and there is no single protocol that has been established. Most studies have sampled the endometrium 3 monthly, and continued medical management if there is a response for up to a year[14].

Similarly long term follow can be difficult. The risk factors that led to the original carcinogenesis are usually still present and with such a high recurrence risk patients need to be encouraged to either undergo immediate fertility treatment or continue with maintenance treatment. The frequency of future endometrial samples and whether office sampling or hysteroscopy is required has not been established. Hysterectomy at some stage following child birth would seem to be sensible as a way of preventing the disease recurring in the long term but when this should be performed and whether the risk of recurrence decreases with weight loss or the menopause is not known. Once recurrence has occurred a number of patients will respond to retreatment. However there are no established guidelines for how many times a patient should be retreated or for how long.

CONCLUSION

An increasing number of patients with either AH or EC will wish to preserve their fertility in the future. These patients need an accurate diagnosis and staging with con-

trast enhanced MRI to minimise their risk of unrecognised concomitant or metastatic disease.

Medical treatment with 400 mg to 800 mg daily of medroxyprogesterone acetate appears to be the best medical management with 3 monthly endometrial sampling to establish response. Treatment can be given for 6 mo to a year and approximately 75% will have a complete initial response with just over 50% having a response without subsequent recurrence. A failed response has theoretical disadvantages of finding more advanced disease but in published studies this is so small as to not be quantifiable.

All these factors need to be taken into consideration when advising a patient about her options but in addition she needs to consider the chances of conception once if treatment is successful. Many patients will be older and have presented with infertility. If the chances of a successful pregnancy are very low at the end of a year hormonal treatment with multiple endometrial samples and uncertainty about the future risk of recurrence then after careful consideration it is possible that the patient will decide to opt for the standard curative treatment of hysterectomy and removal of ovaries.

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