Fertility-sparing treatment in a young patient with complex atypical hyperplasia of the endometrium

Du Toit GC, MBChB, MMed, FCOG(SA), Part-Time Consultant
Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch, Stellenbosch
Correspondence to: George du Toit, e-mail: dutoitg@worldonline.co.za
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Introduction

Endometrial carcinoma is a common gynaecological malignancy in developed countries. It affects postmenopausal women predominantly, but 25% of cases occur in premenopausal women, 5% of whom are younger than 40 years of age.[1] Complex atypical hyperplasia (CAH) of the endometrium is a precursor to endometrial carcinoma, with a progression rate to carcinoma of 10%. Women with stage I, grade 1 endometrial carcinoma treated by hysterectomy, have a 99.2% five-year survival. The high cure rate of the disease shifts the treatment focus to issues of quality of life subsequent to successful treatment.[2] Young nulliparous women with CAH raise the possibility of fertility-sparing treatment. The treatment approach to CAH is viewed in the same light as that pertaining to early-stage endometrial carcinoma. In both scenarios, fertility-sparing treatment (with subsequent successful pregnancies) has been described. The conservative management of CAH poses several challenges with regard to adequate sampling of the endometrium, as well as optimal treatment and follow-up monitoring.[3] The current case illustrates successful conservative management of CAH.

Case study

A 31-year-old nulligravida presented with primary infertility and a long-standing history of oligomenorrhoea. Her menarche occurred at 11 years of age and her medical and surgical history were noncontributory. A clinical examination revealed a weight of 79.1 kg, with a body mass index (BMI) of 25.8. Systemic and gynaecological examinations were within normal limits. Hormone analysis (including thyroid function and prolactin) was normal. A laparoscopy, hysteroscopy and endometrial sampling were performed to assess fertility status. The laparoscopy documented a normal uterus and pelvis. Endometrial histology diagnosed CAH (Figure 1.) The patient received medroxyprogesterone acetate (MPA) 10 mg daily for a month, and a repeat hysteroscopy was performed. At this stage, the endometrium appeared to be atrophic, and sampling was difficult, requiring a resectoscope to obtain endometrial tissue. CAH was present on histology. A levonorgestrel-releasing intrauterine system was inserted and removed three months later. At this stage, the hysteroscopy was normal and histology showed decidual changes in the stroma and a thin atrophic endometrium (Figure 2). Clomiphene citrate ovulation induction was started.

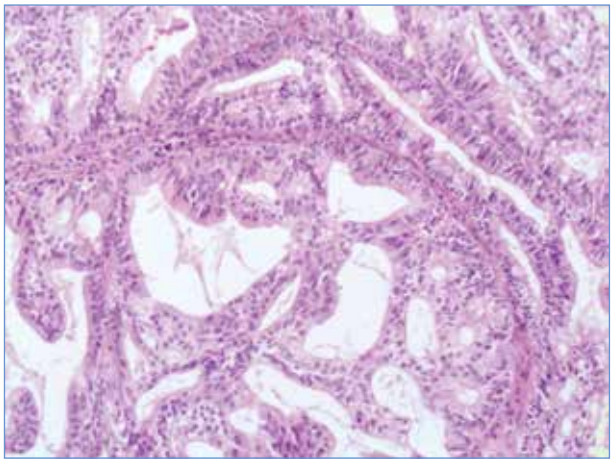

Figure 1: Complex endometrial glandular appearance with back-to-back arrangement and areas with nuclear atypia and occasional mitotic figures

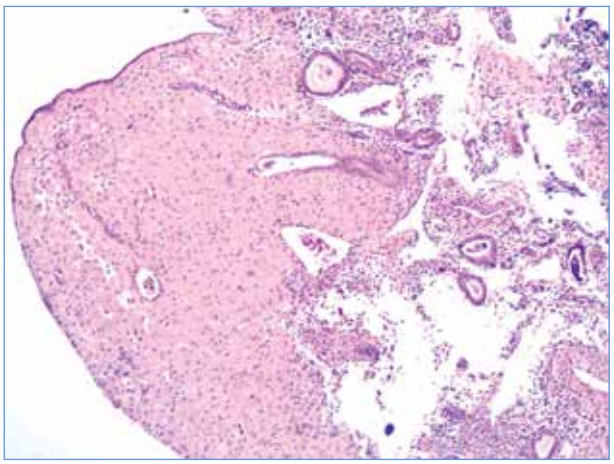

Figure 2: Thin endometrial lining, with desidual changes in the stroma

Discussion

Bokhman divided endometrial carcinoma into two broad categories: stage I and II.[4] Type I tumours comprise low-grade endometrioid carcinomas with good prognosis, and type II tumours represent high-grade carcinomas with poor prognosis.[4] Bokhman's division is based on the clinical, metabolic and endocrine features of the patient. Obesity and chronic anovulation predispose to unopposed oestrogen endometrial stimulation, with proliferation and subsequent hyperplasia.[2] Thus, Bokhman type I tumours are associated with obesity and anovulation. In these cases, hyperplasia commonly coexists with grade 1 endometrial carcinoma. Bokhman type II tumours arise *de novo,* and are less likely to be associated with concomitant hyperplasia. The current case was atypical as the patient had a normal BMI. However, the history of oligomenorrhoea suggests long-standing anovulation.

CAH of the endometrium is a precursor to endometrial carcinoma. Metachronus endometrial carcinoma occurs in 48% of cases.[5] The classification of endometrial hyperplasia is based on the World Health Organization scheme (WHO94). This system, based on a study by Kurman, correlates cytological atypia and glandular complexity with increased risk of carcinoma[6] (Table I).

Fertility-sparing management of CAH requires sensitive and specific pretreatment detection of coexisting endometrial carcinoma. Dilatation and curettage, and Pipelle® endometrial biopsy, both have sampling limitations. Approximately 60% of dilatation and curettage specimens sample less than 50% of the uterine cavity.[5] The flexible Pipelle® device may be deflected by mass lesions, e.g. polyps and myomas, which prevent adequate endometrial sampling. A comparative study on CAH diagnosed by dilatation and curettage and Pipelle® biopsy documented missed carcinoma in 27% and 46%, respectively, in hysterectomy specimens, subsequent to the sampling.[7]

Hysteroscopy does not significantly increase carcinoma detection. Precancerous lesions cannot be visualised with hysteroscopy. Hysteroscopic appearances cannot distinguish between CAH and carcinoma. Transvaginal ultrasonography measurement of an endometrial thickness of 5 mm or more has been shown to detect 95% of endometrial carcinomas in postmenopausal women.[8] The overlap of normal endometrial thickness with carcinoma limits the value of ultrasound in premenopausal women. Histochemical markers, e.g. oestrogen and progesterone receptors or phosphatase and tensin homolog gene expression, may serve as predictors to treatment response, but prospective data are lacking.[1,9]

Fertility-sparing management of CAH aims to completely reverse the pathology to normal endometrial function and prevent progression to endometrial cancer. Progesterone counterbalances the mitogenic effects of oestrogen and induces secretory differentiation of the endometrium. Currently, the dose, type, schedule and optimal route of progesterone administration remains to be determined. The available formulations are represented in Table II.

Table II: Hormonal treatment of atypical endometrial hyperplasia

Treatment	Dosage or length
Medroxyprogesterone acetate	10-20 mg daily, or cyclic 12-14 days per month
Depot medroxyprogesterone	150 mg intramuscularly, every three months
Micronised vaginal progesterone	100-200 mg daily, or cyclic 12-14 days per month
Megestrol acetate	40-200 mg daily
Levonorgestrel-containing intrauterine device	1-5 years

Table I: Progression rates of precursor lesions of the endometrium[6]

Pathology	Number of patients (n = 170)	Number that regressed (%)	Number that persisted (%)	Number that progressed to carcinoma (%)
Simple hyperplasia	93	74 (80)	18 (19)	1 (1)
Complex hyperplasia	29	24 (80)	5 (17)	1 (3)
Simple atypical hyperplasia	13	9 (69)	3 (23)	1 (8)
Complex atypical hyperplasia	35	20 (57)	5 (14)	10 (29)

Regression of hyperplasia has been observed in 80-90% of individuals receiving MPA at a dose of 10 mg daily for 12-14 days per month. Systemic progestin side-effects include water retention and mastalgia. The levonorgestrel-releasing intrauterine system and micronised vaginal progesterone provide alternatives to oral therapy. The vaginal route negates the systemic side-effects and enhances compliance. Several studies have documented the efficacy of the levonorgestrel-releasing intrauterine system. These studies include cases with well differentiated endometrial carcinomas. Post-treatment sampling of the endometrium reveals CAH regression in up to 100% of cases, and carcinoma regression in up to 70%.[10] Because of atrophy that is induced by progestin, sampling may be difficult. In the current case, a resectoscope was used to obtain tissue after initial therapy. Hormonal resistance may occur in 30% of cases. On regression of CAH, the underlying hormonal cause, e.g. anovulation, should be appropriately addressed. In the current case, ovulation induction with clomiphene citrate was used. Meticulous follow-up is warranted as recurrence of hyperplasia occurs in 30% of cases.[11] These relapses can be successfully re-treated, but require adequate follow-up and resampling.[1] An alternative to progestin therapy is gonadotropin-releasing hormone agonist treatment, which has a success rate of 85%. Systemic side-effects, e.g. hot flushes, limit its use.

Conclusion

The current case of CAH illustrates the management principles of conservative treatment to retain fertility. The pivotal role of adequate pretreatment sampling and post-treatment evaluation of the endometrium is underscored by the use of a resectoscope to obtain tissue after initial treatment. The case further documents the fact that progestin treatment is the treatment of choice. The levonorgestrel-releasing intrauterine system offers adequate progestin exposure of the endometrium, without systemic side-effects. Fertility-sparing CAH treatment requires meticulous pretreatment evaluation to exclude invasive carcinoma, as well as post-treatment surveillance to detect recurrence.

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