ONCOLOGY

Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma

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OBJECTIVES: This study evaluated fertility and oncological outcomes in women with complex atypical hyperplasia (CAH) or nonmyoinvasive grade 1 endometrioid endometrial carcinoma (EM) who desired fertility-sparing therapy.

STUDY DESIGN: The retrospective cohort study included women younger than 45 years with CAH or EM who desired fertility-sparing treatment at our institution. Only patients for whom both oncological treatment and pregnancy outcomes were available were included. Statistical analyses were performed using a Fisher exact test, Pearson χ^2 test, and Spearman rank correlation test, as appropriate.

RESULTS: Seventy-five patients were identified, and 23 (13 CAH, 10 EM) met the inclusion criteria. All 23 patients had at least 1 prior pregnancy. Treatment was split between oral progesterone only (38.5% CAH, 40% EM), levonorgestrel intrauterine device only (30.8% CAH, 20% EM), and both (30.8% CAH, 40% EM). After a median follow-up of 13 months (range, 3—74 months), 9 patients (46.2% CAH, 30% EM, $P = .39$) had persistent/progressive disease. Eight patients (30.8% CAH, 40% EM, $P = .69$) ultimately had a hysterectomy, and 3 of these (13.0%) were found to have persistent/progressive disease. Median time from diagnosis to hysterectomy was 13 months (range, 4—56 months). Fourteen of the 23 patients utilized assisted reproductive techniques (60.9%); 12 underwent IVF and 2 chose a gestation carrier. Seven clinical intrauterine pregnancies (30.4%) resulting in 6 live births (26.1%) were found in the entire cohort.

CONCLUSION: Fertility-sparing treatment for CAH and grade 1 endometrial cancer is feasible with progestin therapy and leads to clinically meaningful rates of pregnancy in young women who desire fertility.

Key words: endometrial cancer, endometrial hyperplasia, fertility-sparing treatment, progestin therapy

Cite this article as: Kudesia R, Singer T, Caputo TA, et al. Reproductive and oncologic outcomes after progestin therapy for endometrial complex atypical hyperplasia or carcinoma. Am J Obstet Gynecol 2014;210:255.e1-4.

In the United States, endometrial cancer is the most common gynecological malignancy and accounts for 6% of all cancers in women, with a 2.5% lifetime risk.[1] In 2013, the National Cancer Institute estimates 49,560 new cases in the United States and 8190 deaths.[2] The majority of patients are postmenopausal, and the average age of diagnosis is 61 years.

However, grade 1 endometrioid endometrial cancer (EM) or its precursor lesion, complex atypical hyperplasia (CAH), can still affect premenopausal women, particularly those with risk factors of obesity, polycystic ovarian syndrome, and infertility. Some of these women desire retention of fertility, in which case, standard surgical treatment, comprising hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection, is unacceptable. As this situation becomes more common with increasing rates of obesity and delayed childbearing, there is a greater need for fertility-sparing treatments.[3,4]

Options for patients with EM or CAH who desire fertility preservation include the following: egg/embryo freezing prior to hysterectomy, progestin treatment followed by use of assisted reproductive technologies (ART), or hysterectomy with lymph node dissection and preservation of ovaries with the future use of a gestational carrier.

Progestin therapy is most commonly used to allow a disease-free window in which to attempt pregnancy. This approach has been evaluated and found viable in small studies[5-12] and literature

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Received Aug. 6, 2013; revised Oct. 17, 2013; accepted Nov. 4, 2013.

This study was supported by the Department of Obstetrics and Gynecology, Weill Cornell Medical College—New York Presbyterian Hospital.

The authors report no conflict of interest.

Presented at the 14th Biennial Meeting of the International Gynecologic Cancer Society, Vancouver, BC, Canada, Oct. 13-16, 2012, and the 59th Annual Scientific Meeting of the Society for Gynecologic Investigation, San Diego, CA, March 21-24, 2012.

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reviews.[13-16] More recently, 3 meta-analyses have pooled these data, yielding complete resolution rates ranging from 65.8% to 74% for CAH and 48.2% to 72% for EM patients.[17-19] The available data suggest relative safety and efficacy of progestin treatment for a short window to allow the woman to achieve her reproductive goals.

Few studies have evaluated the pregnancy outcomes or barriers to successful childbearing in this patient population. The objective of this study was to evaluate the oncological and reproductive outcomes in young women with CAH or EM at our institution.

Materials and Methods

This retrospective case-controlled cohort study included women younger than 45 years with CAH or EM (grade 1 endometrioid only) who desired fertility-sparing management. Institutional review board approval was obtained. Patients were identified through hospital billing and pathology databases. Only patients for whom both oncological and pregnancy outcomes were available were included in the study.

All patients with EM underwent a pelvic magnetic resonance imaging to confirm that there was no myometrial invasion or extrauterine disease prior to initiating progestin therapy. Medical records were reviewed for demographic information, pathological and treatment information, and pregnancy data including usage of ART. In patients who utilized ART, stimulation protocols, endometrial imaging studies, and any other information in their in vitro fertilization (IVF) records were also reviewed.

Primary outcomes included regression of disease vs persistence or progression, need for hysterectomy, length of follow-up, IVF cycle outcome, and pregnancy outcomes. For those patients who underwent hysterectomy, length of treatment between diagnosis, and hysterectomy was also evaluated.

Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC). The Fisher exact test, Pearson χ^2 test, and Spearman rank correlation test were utilized as appropriate.

Results

Of the 75 patients identified, 23 (13 CAH, 10 EM) met the inclusion criteria and for whom both the oncological and pregnancy data were available. There were no significant demographic differences between the CAH and EM groups (Table 1). The average age was 38.5 ± 4.4 years in the CAH group and 38.5 ± 4.2 years in the EM group ($P = .98$). All 23 patients had at least 1 prior pregnancy. All 13 patients with CAH were nulliparous; 2 patients with EM (20%) had a prior live birth. There was no difference between the 2 groups in distribution of gravidity and parity ($P = .31$ for gravity, $P = .18$ for parity). Body mass index was not correlated with severity of pathology ($r_s = -0.0972$, $P = .69$).

Treatment was split between oral progesterone only (38.5% CAH, 40% EM), levonorgestrel intrauterine device only (30.8% CAH, 20% EM), and both oral and intrauterine progesterone (30.8% CAH, 40% EM) (Table 2). The number of patients for each treatment regimen did not vary significantly between the 2 groups; $P = 1.0$, $P = .66$, and $P = .69$ for oral only, intrauterine device only, and combined regimens, respectively. The most common oral progesterone prescribed by the gynecological oncologists was megestrol acetate, 160-240 mg daily in divided doses. Patients underwent endometrial sampling by office biopsy or dilation and curettage every 3 months. Those who had persistent or worsening disease after 12 months of progestin therapy were considered to have failed fertility-sparing treatment.

After a median follow-up of 13 months (range, 3–74 months), 9 patients (46.2% CAH, 30% EM, $P = .39$) had persistent or progressive disease. Eight patients (30.8% CAH, 40% EM, $P = .69$) ultimately had hysterectomy: 7 with persistent disease and 1 who had complete resolution but requested definitive management. Two patients with persistent disease declined hysterectomy. Among the patients who had a hysterectomy, 3 (13.0%) had higher-grade disease on the final specimen: 2 grade II and 1 focal clear cell features. No patient was found to have extrauterine disease. Median time from diagnosis to hysterectomy was 13 months (range, 4–56 months).

Fourteen patients ultimately attempted pregnancy by using ART. Two patients received care outside our institution and both had children via gestational surrogates. Twelve had IVF at our center, 8 (61.5%) in the CAH group, and 4 (40%) in the EM group ($P = .08$). Eleven initiated their first cycle within 24 months of initial diagnosis; 1 patient waited 5 years. The mean age at oocyte retrieval was 40.0, and the mean peak endometrial stripe was 9 mm. Among the 12 patients who underwent IVF, 5 clinical intrauterine pregnancies (41.7%) and 4 live births (33.3%) resulted. Including the 2 gestational surrogate pregnancies, the total live birth rate was 26.1% in this study.

Barriers to childbearing were also analyzed. Of 23 patients who had fertility consultation, 9 (38.1%) ultimately did not proceed. The most common reason (5 of 9, 55.5% patients) was persistent or progressive pathology. Three patients (33.3%) electively stopped treatment for unclear reasons, and 1 patient (11.1%) cited prohibitive cost of ART treatment.

Comment

As compared with previously published reports, our data are consistent regarding the efficacy of fertility-sparing treatment for complex atypical hyperplasia and grade 1 endometrial cancer with progestin therapy. Given that 40% of patients with a CAH diagnosis have invasive cancer at the time of hysterectomy and that 10% of those have deep myometrial invasion, it is not clear how many patients in our CAH cohort actually had disease progression on progestins.[20]

In 2010, 22.1% of IVF cycles for all causes in women aged 38-40 years resulted in live birth.[21] Despite an overweight, advanced maternal age patient population in our study, the live birth rate in the IVF group was greater than 30%, which is higher than the national IVF success rates. This finding mitigates concern over any permanent pathological effect on the endometrium and