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Nonoperative management of atypical endometrial hyperplasia and grade 1 endometrial cancer with the levonorgestrel intrauterine device in medically ill post-menopausal women☆

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HIGHLIGHTS

- Postmenopausal women tolerate the levonorgestrel intrauterine device well.
- 50% of women converted to benign endometrium, but several later developed AH/EC.
- Treatment decreases endometrial PR expression, particularly in women who respond.

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ABSTRACT

Objective. To assess the endometrial response rates to treatment with the levonorgestrel intrauterine device in post-menopausal women with atypical hyperplasia/endometrial intraepithelial neoplasia and grade 1 endometrioid (AH/EC) endometrial carcinoma who are not surgical candidates.

Methods. Chart review was undertaken of patients with AH/EC who underwent levonorgestrel intrauterine device insertion by a gynecologic oncologist within two academic health systems between 2002 and 2013. When available, tissue blocks were evaluated with immunohistochemical staining for progesterone receptor expression.

Results. A total of 41 patients received treatment for AH/EC with the levonorgestrel intrauterine device. Follow up sufficient to assess response occurred in 36 women (88%). Complete response was documented in 18 of 36 women (50%), no response in 8 patients (22%), partial response in 3 women (8%) and progression of disease in 7 patients (19%). Four of 18 patients with complete response (22%) later experienced relapse of hyperplasia or cancer. Four patients (10%) died during the study period: none had evidence of metastatic disease and 1 of the 4 woman died of perioperative complications following hysterectomy for stage I disease. Patients responding to treatment had significantly lower progesterone receptor expression on post-treatment biopsies.

Conclusions. Intrauterine levonorgestrel is a viable treatment option for post-menopausal women with AH/EC who are poor candidates for standard surgical management. The response rate in this series is similar to published reports in premenopausal patients and includes cases of disease recurrence following conversion to benign endometrium.

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AH	Atypical hyperplasia
EIN	Endometrial intraepithelial neoplasia
EC	Grade 1 endometrioid endometrial carcinoma
IUD	Intrauterine device

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1. Introduction

Endometrial cancer is the most common of the gynecologic malignancies, with more than 60,000 new diagnoses expected in the United States in 2016 [1]. Endometrioid adenocarcinoma, the most common type, is typically an estrogen driven disease affecting obese women. Estrogen excess, regardless of the source, results in premalignant endometrial neoplasia [atypical hyperplasia (AH) or endometrial intraepithelial neoplasia (EIN)], and endometrial carcinoma (EC). Progesterone is an ovarian steroid which antagonizes estrogen mediated proliferation of the endometrial glands during the latter half of the menstrual cycle, leading to secretory changes and eventual sloughing of the glands with attendant decidualization of the endometrial stroma. Lack of progesterone inhibition of estrogen stimulation of the endometrium is associated with the development of endometrial neoplasia. This phenomenon may occur in premenopausal women with anovulatory disorders [2,3], or in post-menopausal women with estrogen excess due to unopposed estrogen, obesity, or insulin resistance [4,5].

Treatment with progesterone can reverse the neoplastic changes in the endometrium caused by unopposed estrogen stimulation. Progesterone treatment has also been used in the setting of metastatic or recurrent disease. For AH/EIN or carcinoma in a premenopausal woman, progesterone may be used for the purposes of fertility preservation. Retrospective studies and numerous published case reports have demonstrated high conversion rates to normal endometrium following progesterone treatment in premenopausal women, with subsequent successful pregnancies [6–8]. Prospective trials using progesterone IUDs are currently being conducted to better characterize the success rates of this treatment [9].

There are fewer data, however, supporting the use of primary progesterone therapy in post-menopausal women who develop AH/EIN or endometrial cancer. For these women, surgery (total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy) is considered the standard of care treatment. Unfortunately, not all women will be candidates for surgery. Obesity, diabetes, and hypertension are associated with increased risk of endometrial cancer as well as increasing perioperative morbidity and mortality. There is a subset of post-menopausal women with endometrioid endometrial cancer for whom the risks of general anesthesia and pelvic surgery are too significant. For these women, the option of systemic or intrauterine progesterone treatment may be a safer alternative to surgery without the toxicity associated with radiation therapy.

There are no existing large studies of primary progesterone treatment focused on post-menopausal patients to guide therapy. Early studies are conflicting but hormonal response rates in patients with AH/EIN may be lower following menopause [10,11]. Older age is associated with lower likelihood of complete response among premenopausal women with AH/EIN or grade 1 EC using oral progestin to attempt fertility preservation [12]. Most published series include both pre- and post-menopausal patients, with the majority of patients premenopausal, and data specific to the post-menopausal cohort is not separately reported with the exception of FJ Montz's prospective study of 16 patients with a progesterone-containing intrauterine device(IUD) (Progestasert; ALZA Corp, Mountain View, Calif) [13]. This pilot study using the Progestasert device (which is no longer commercially available) enrolled medically ill women with grade 1 endometrioid cancer and compared them to a historical cohort of matched patients managed surgically. Dr. Montz reported 9 of 12 patients (75%) with conversion to negative endometrial biopsies following IUD insertion and no disease related deaths in the study population. Perioperative complications were common within the matched historical control patient cohort and 1 perioperative death occurred in that group of surgically managed patients [13].

While Montz's study did suggest an acceptable response rate to intrauterine progesterone in the post-menopausal woman, there are theoretical concerns regarding the longevity of success of progesterone treatment in this setting. Data from GOG 211 demonstrated that even short duration of treatment with progesterone in post-menopausal women with endometrial cancer resulted in a down regulation of the progesterone receptor (PR), presumably leading to a lack of progesterone efficacy [14]. In the premenopausal patient who wishes to preserve fertility, this is less of a concern as a hormonal cycle can be created with oral contraceptives or the progesterone associated with a subsequent pregnancy, but the post-menopausal patient treated with progesterone requires long term progesterone effect to prevent disease recurrence.

The gynecologic oncologists at the University of Virginia and the University of North Carolina care for patients from a region where obesity rates are high and medical co-morbidities are often unaddressed due to lack of access to care. As we care for a relatively large percentage of patients with endometrial cancer who are poor surgical candidates, we undertook the current study to examine the feasibility and success rates of progesterone treatment with the levonorgestrel IUD specifically in these post-menopausal women. We examined patients from the clinical practices of oncologists at two institutions; reasons for choosing intrauterine hormonal management over radiation or surgical management varied and patients were managed without a protocol and all management decisions were made for clinical rather than research purposes. Given the concern regarding progesterone receptor down regulation raised by GOG 211, we also sought to describe the effect of the levonorgestrel IUD on progesterone receptor expression in these women planning long term progestin therapy.

2. Methods

Following approval by the respective institutional review boards of each institution all women who underwent levonorgestrel IUD insertion within the divisions of gynecologic oncology at the University of Virginia (Charlottesville, VA, USA) and the University of North Carolina (Chapel Hill, NC, USA) during the study period were identified using billing data. Patients with diagnoses of “complex hyperplasia (CH)”, “complex atypical hyperplasia” (CAH), AH/EIN, or EC underwent further review. These criteria included diagnostic terms from both the 1994 and 2014 World Health Organization's classification systems for endometrial hyperplasia because the study period spanned both systems. All cases were reviewed by a gynecologic pathologist (A.M.M.) and, when outdated terminology was used in the original diagnosis, reclassified according to the current, two-tiered WHO terminology (hyperplasia without atypia versus AH/EIN). Each patient's clinical documentation was reviewed in institutional electronic medical records including scanned documents sent by referring clinicians. Data abstracted included age at diagnosis, hyperplasia or tumor characteristics including grade and histology, imaging studies obtained during treatment, body mass index (BMI), documented medical comorbidities, pathology reports of all available endometrial biopsies, curettage, or excisional procedures, and available reports from any radiotherapy treatments or surgical procedures. This retrospective review consists of patients not enrolled in a formal investigational protocol and treatment regimens including prior use of hormonal therapy and dosages were at the discretion of the treating physicians, but only patients treated with insertion of a levonorgestrel IUD were included in the analysis. There was no uniform protocol for pretreatment imaging or evaluation but all patients with cancer were initially felt to have clinical stage I disease. All pathology was reviewed by the pathologists at the respective institutions.

Complete response was defined as benign endometrium without hyperplasia on subsequent endometrial sampling following treatment with any form of progestin whether systemic or intrauterine. Partial response was defined as hyperplasia without atypia following treatment of AH/EIN or hyperplasia without atypia or AH/EIN following treatment of carcinoma. No response is defined as persistence of the initial tissue diagnosis on subsequent tissue sample. Progression was defined as any grade carcinoma following treatment of AH/EIN or grade 2 or higher carcinoma following treatment of grade 1 carcinoma. These definitions

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