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REVIEW ARTICLE

Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer

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ABSTRACT

Background: Definitive management with hysterectomy could be appropriate for some patients with endometrial cancer and its precursor lesions, but poses challenges for those desiring future fertility. *Objectives:* To review risk factors for endometrial hyperplasia/cancer among premenopausal women and discuss management options for fertility preservation. *Search strategy:* A literature search through the PubMed, Ovid, and Cochrane databases was conducted using the terms "endometrial hyperplasia" and "endometrial cancer," cross-referenced with "fertility preservation." *Selection criteria:* All articles published in English between January 1, 2000, and January 1, 2015, were considered if they were readily available online. *Data collection and analysis:* Articles were analyzed and information was synthesized into a comprehensive review. *Main results:* Chronic anovulation, obesity, polycystic ovarian syndrome, metabolic syndrome, insulin resistance, and type 2 diabetes mellitus must be appreciated as risk factors for endometrial pathology. Providers must exert vigilance in identifying patients at risk and in initiating pre-emptive strategies. Risk reduction with lifestyle modification, weight loss, and glycemic control can improve regression and overall health. Fertility outcomes for these patients are promising, especially with assisted reproductive technology. *Conclusions:* Conservative management could be appropriate for carefully selected women with complex atypical endometrial hyperplasia or early-stage endometrial cancer who desire future fertility.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in high-income countries and the fourth most common cancer in women of all ethnic origins, affecting approximately 23.5 per 100 000 women [1]. Among affected women, 25% are premenopausal and 2.5%–14.4% are younger than 40 years at diagnosis [2]. The vast majority (84%) of endometrial cancers are well-differentiated type 1 endometrioid adenocarcinomas that are associated with prolonged, unopposed estrogen exposure and conditions such as obesity, diabetes mellitus, and hypertension [3]. The rest of the cases are classified as type 2, which is predominantly of serous histopathology and has a different etiology and a worse prognosis than does the endometrioid variant [1].

In the setting of prolonged, unopposed estrogen exposure, the endometrium can become disordered, resulting in endometrial hyperplasia. Endometrial hyperplasia is a cancer precursor lesion that, if left untreated, has a high likelihood of progression to endometrial cancer. Recognized risk factors for elevated estrogen levels relative to progesterone are nulliparity, late age at menopause, menstrual irregularity, obesity, type 2 diabetes, polycystic ovarian syndrome (PCOS), and metabolic syndrome. Up to 43% of patients with endometrial hyperplasia and cytologic atypia harbor a coexisting carcinoma, and the identification and prompt management of endometrial pre-cancers should be taken seriously by both patients and practitioners [2].

Whereas hysterectomy remains the gold-standard definitive management strategy for these pathologies, management options are less clear for premenopausal women who are interested in retaining future fertility potential. Conservative fertility-preserving interventions have been described that allow women the opportunity of completing childbearing before hysterectomy. The present review seeks to provide practitioners with information regarding the diagnosis, counseling, and management of endometrial cancer and endometrial hyperplasia in at-risk populations of reproductive age who are seeking fertility preservation at the time of diagnosis.

2. Materials and methods

A comprehensive search of the primary literature was performed through the PubMed, Ovid, and Cochrane databases using the search terms "endometrial hyperplasia" and "endometrial cancer." These terms were cross-referenced with "fertility preservation." All articles published between January 1, 2000, and January 1, 2015, were considered in the analysis. Non-English articles, articles that were not readily available online, and articles deemed irrelevant by the investigators

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were excluded. The articles were analyzed and information regarding endometrial hyperplasia and endometrial cancer was synthesized into a comprehensive review focusing on the management of premenopausal patients who desire fertility-preserving therapy.

3. Results

3.1. Histologic precursors to endometrial cancer

The true incidence of the various types of endometrial hyperplasia in the general population is unknown; the estimated prevalence is as high as 132 per 100 000 woman-years [3]. Many classification systems for endometrial hyperplasia have been described over the past 60 years [4]. The most widely used is the WHO 1994 classification system, which is largely based on a study by Kurman et al. [5] published in 1985 that correlated cytologic atypia with the risk for endometrial cancer in 170 patients with endometrial hyperplasia who were followed up for at least 12 months [6]. It is from this classification system that the popular "penny, nickel, dime, quarter" rule was developed, which refers to the respective risks of progression to cancer being 1%, 3%, 8%, and 29% for simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia, and complex atypical hyperplasia (CAH) [7]. Briefly, the degree of crowding and architectural abnormality determined whether the endometrial hyperplasia was classified as simple or complex whereas the absence or presence of nuclear atypia (hyperchromasia, high nuclear to cytoplasmic ratio, and prominent nucleoli) determines whether the lesion is classified as atypical. In general, the degree of architectural abnormality coincides with the extent of cytologic atypia, such that greater complexity is invariably associated with nuclear atypia. Nevertheless, the assessment of many of these histological features is subjective, with a high degree of interobserver variability even among expert gynecologic pathologists.

Aside from having poor diagnostic reproducibility, the WHO 1994 classification system had several other inherent shortcomings. It was not subjected to rigorous verification and is based on only one study with a small sample size. In recognition of these failings, the most recent update to this system (WHO 2014) [8] proposes a two-tiered classification system in which cases are divided into non-atypical (benign) hyperplasia (Fig. 1) and atypical hyperplasia (Fig. 2). An alternate system, proposed by the International Endometrial Collaborative Group, divides lesions into benign hyperplasia and endometrial intraepithelial neoplasia [9]. Although not as widely used as the WHO system, it has been endorsed by a number of organizations, including the Society for Gynecologic Oncology's Clinical Practice Committee, and is also supported by WHO as an alternate classification system. For the purposes of the present review, "CAH" refers to complex hyperplasia with atypia (atypical hyperplasia) as defined by WHO.

3.2. Risk factors for endometrial hyperplasia and cancer

Obesity can be related to 40%–50% of endometrial cancers [10]. Women with a body mass index (BMI) of more than 30 (calculated as weight in kilograms divided by the square of height in meters) have a fourfold increased risk of endometrial hyperplasia, and women with a BMI of more than 40 have a 13-fold increased risk [10]. Obese women are more likely to have a relapse after initial treatment of complex endometrial hyperplasia or early-stage endometrial cancer. Gallos et al. [11] found that women with a BMI of less than 35 had a 3.3% relapse rate after receiving a levonorgestrel-releasing intrauterine system (IUS) compared with a rate of 32.6% among women with a BMI of 35 or more. Treatment of obesity reduces, but does not eliminate, the risk for endometrial lesions associated with a high BMI [12].

Type 2 diabetes mellitus is also a recognized risk factor for endometrial pathology. In women with diabetes, the risk of endometrial cancer developing from endometrial hyperplasia is doubled and quadrupled, respectively, compared with BMI- and age-comparable women without diabetes [10,13,14]. As obesity becomes more prevalent, the incidence of diabetes mellitus is also likely to increase, with some estimates predicting an increase of 179%–351% within 50 years [13]. The endometrium acts as a target for insulin and insulin inhibits endometrial decidualization. Insulin also stimulates ovarian and adrenal androgen production and acts as an endometrial mitogen by increasing the action of insulin growth factor on the endometrium [15]. There is some evidence that metformin, a commonly used insulin sensitizer, could decrease the risk of endometrial cancer by increasing peripheral insulin uptake [10,16].

Moreover, an increased risk for endometrial pathologies is well described in women with PCOS, a common endocrinopathy that affects 6%–10% of all women of reproductive age. Random biopsy of the endometrium of women with PCOS reveals the presence of endometrial hyperplasia in as many as 48.8% of cases.

Finally, metabolic syndrome—characterized by central obesity, hyperglycemia, hypertension, and dyslipidemia—is associated with an increased likelihood of endometrial pathology beyond that associated with isolated risk factors [17]. In 2007, the World Cancer Research Fund reviewed the available evidence on nutrition, lifestyle modification, physical activity, and prevention of cancer and highlighted the importance of healthy living for the prevention of endometrial cancer [18].

3.3. Pathophysiology of endometrial hyperplasia and cancer

Endocrine and paracrine contributions to endometrial pathology are well recognized. Endometrioid precancerous lesions result from prolonged and excessive exposure of the endometrium to estrogen without opposition by progesterone, which normally helps to inhibit endometrial proliferation and induces differentiation and decidualization.

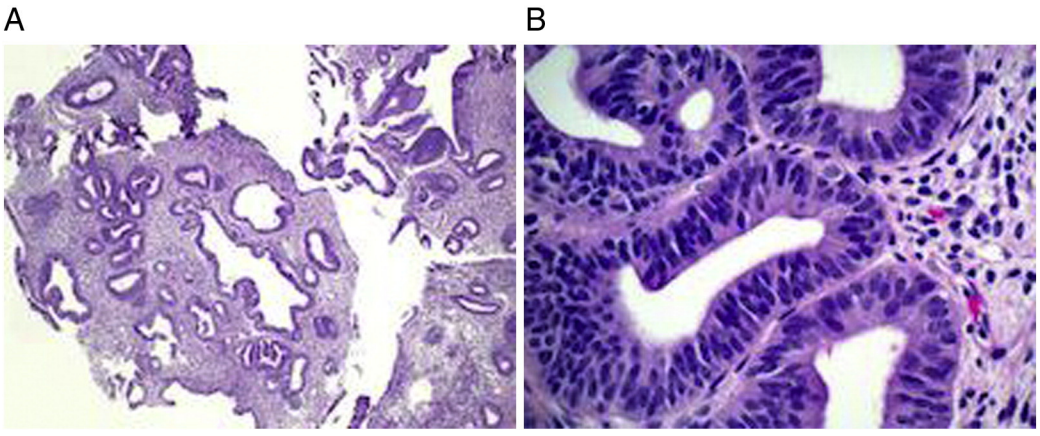

Fig. 1. Benign hyperplasia. At low magnification (A; 40×), there is architectural disorder with occasional dilated and budded glands with focal crowding such that the glandular element is slightly in excess of the stroma. Higher magnification (B; 400×) shows pseudostratified uniform nuclei with inconspicuous nucleoli. Significant atypia is not identified.

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