



## Original Article

## Endometrial Cancer After Endometrial Ablation vs Medical Management of Abnormal Uterine Bleeding

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**ABSTRACT** **Study Objective:** To investigate whether endometrial ablation is associated with increased risk or delayed diagnosis of endometrial cancer compared with medical management of abnormal uterine bleeding.

**Design:** Multi-centered retrospective cohort study (Canadian Task Force classification II-2).

**Setting:** The study was performed using data from The Health Improvement Network, a representative population-based cohort of patients in 495 outpatient general practitioner practices in the United Kingdom.

**Patients:** Women aged >25 years with abnormal uterine bleeding diagnosed between June 1994 and September 2010.

**Interventions:** Endometrial ablation, medical management, or both.

**Measurements and Main Results:** A total of 234 721 women met study inclusion and exclusion criteria, 4776 of whom underwent endometrial ablation and the remaining 229 945 received medical management. Cox models compared endometrial cancer rates between ablation and medical management groups using hazard ratios. To investigate a possible diagnostic delay, the median time from bleeding diagnosis to endometrial cancer diagnosis in women in whom endometrial cancer developed was compared using the Mann-Whitney *U* test. All statistical tests were 2-tailed, with  $\alpha = .05$ . During a median observation period of 4.07 years (interquartile range [IQR], 1.88–7.17), endometrial cancer developed in 3 women in the ablation group and 601 women in the medical management group (ablation hazard ratio, 0.45; 95% confidence interval, 0.15–1.40;  $p = .17$ ). Median time to diagnosis was 237 in the ablation group, and 299 days in the medical management group (ablation IQR, 155–1350; medical management IQR, 144–1133.5;  $p = .99$ ). Adjusted and sensitivity analyses did not change the results.

**Conclusions:** No difference was observed in endometrial cancer rates, and there was no delay in diagnosis when comparing endometrial ablation vs medical management. Further studies are needed to investigate the effect of previous ablation exposure on histology or cancer stage at manifestation of endometrial cancer. *Journal of Minimally Invasive Gynecology* (2014) ■, ■–■ © 2014 AAGL. All rights reserved.

**Keywords:** Endometrial ablation techniques; Endometrial neoplasms; Menorrhagia; Uterine neoplasms

**DISCUSS** You can discuss this article with its authors and with other AAGL members at <http://www.AAGL.org/jmig-21-4-JMIG-D-13-00662>



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The authors declare no conflicts of interest.

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The lifetime prevalence of abnormal uterine bleeding (AUB) is nearly 30%, and is defined as “bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing” [1]. The effectiveness of minimally invasive surgical techniques and devices vs medical management of AUB has been well studied and summarized in a meta-analysis [2] of 10 randomized comparative effectiveness trials [3–12]. Although this meta-analysis showed improvement in bleeding after ablation, there are limited data insofar as adverse effects and device safety. Only 1 small study ( $n = 79$ ) has assessed adverse events after 1 year, and found 1 instance of infection in the medical management arm [11]. None of these randomized studies measured adverse outcomes in real-world clinical use or in a population-based cohort.

Endometrial cancer is the fourth most common cancer in women [13] and is a potential adverse outcome of treatment of AUB; several case reports of endometrial cancer after endometrial ablation have been published [14–24]. These authors have hypothesized that all forms of ablation may contribute to endometrial cancer via several shared biologic mechanisms. AUB can be caused by hormonal irregularities such as anovulation, which increases endometrial cancer risk because of endogenous unopposed estrogen [25,26]. Progestins, present in medical management treatment of AUB, have a protective effect against endometrial cancer [27,28]. Women who choose ablation over medical management would not receive this protective effect of progestins and could be at increased relative risk of endometrial cancer. In addition, intrauterine scarring from ablations may increase endometrial cancer risk owing to increasing cell turnover [24]. Intrauterine scarring may also mask the findings of endometrial cancer and delay its diagnosis by preventing outflow of blood from the uterine cavity [29], a common clinical hallmark of endometrial cancer that prompts biopsy. Furthermore, intrauterine scarring may make biopsy specimens less sensitive for detection of underlying malignancy. Such delay may lead to more advanced stage cancers, with higher mortality [30]. The alternative remains that ablation may destroy premalignant cells, which are vulnerable to ablation techniques, and instead reduce the risk of endometrial cancer. These hypotheses have been investigated only in underpowered studies with inadequate or absent controls [31–33].

The objective of the present study was to use a large database of real-world clinical data to compare endometrial cancer rates and time to diagnosis in women with AUB treated with endometrial ablation vs medical management. We hypothesized that ablation would be associated with an increased rate of endometrial cancer and delay its diagnosis.

## Material and Methods

The Investigational Review Board at the University of Pennsylvania (case No. 813152) exempted this study because of its use of an anonymized database, and the UK Scientific Review Committee (reference No. 11-021) approved the study.

## Study Design

This retrospective cohort study investigated women with a diagnosis of AUB included in a UK-based clinical database, The Health Improvement Network (THIN), privately owned by Cegedim Strategic Data (London, UK), a data vendor and electronic medical record software supplier of Vision to UK general practitioners (GPs). Nearly identical to the public General Practitioner Research Database (GPRD), it reports data, diagnostic Read codes, and Multilex drug classification on more than 9 million patients [34]. These hierarchical Read codes are used for clinical rather than billing purposes and are therefore less susceptible to rule-out or up-diagnosis observed in studies using *International Classification of Diseases*, 9th revision (ICD-9) codes [34]. Like the GPRD, THIN is generalizable to the entire UK population [35] and accurately reports data on chronic diseases [36] and diagnoses such as cancer [37].

Women aged  $>25$  years with AUB diagnosed between June 1994 and September 2010 were included. AUB clinical Read codes were generated with widely accepted code generation methods [38] and were based on ICD-9 and ICD-10 billing codes for menstrual bleeding disorders evaluated in previous investigations in other UK databases [35].

Women were examined 90 days after the incident diagnosis of an AUB episode of care to assess exclusion criteria. Women with a diagnosis of endometrial cancer, myomas, or polyps made during the AUB episode of care were excluded to achieve a cohort of women with a true incident AUB diagnosis who would be equally eligible to undergo either endometrial ablation or medical management. Women who underwent hysterectomy, were transferred from the practice, or died during the episode of care were excluded because they were no longer at risk for endometrial cancer.

## Data Collection

All women underwent endometrial ablation or medical management, or both, because of AUB. Given the shared biologic mechanisms for endometrial cancer risk modification, endometrial ablation was defined to include first-generation resectoscopic transcervical resection of the endometrium or second-generation endometrial ablation using various devices. Medical management included expectant treatment, combination estrogen-progestin and progestin-only hormone therapy, or other nonhormone therapies such as nonsteroidal anti-inflammatory drugs or anti-fibrinolytic agents. Treatments were initially assigned during the 90-day AUB episode of care, counting women with an observed ablation Read code as undergoing endometrial ablation and the remaining women as undergoing medical management. As-treated analysis was performed to account for crossover in treatment regimens over time. Specifically, if a woman received medical management and later underwent endometrial ablation, she contributed medical management observation time until the ablation procedure and then contributed the remainder of

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