

# Endometrial Cancer Incidence in Patients With Atypical Endometrial Hyperplasia According to Mode of Management

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**Abstract.** *Background/Aim:* It is well established that around one-third of patients with atypical endometrial hyperplasia (AEH) go on to develop endometrial cancer (EC). *Patients and Methods:* This retrospective cohort study included 119 patients recruited from the University Hospitals of Leicester from 01/01/2015 to 01/01/2020 with a diagnosis of AEH by endometrial biopsy. Patients were divided into two groups according to the management modality: Primary surgery (n=99), and conservative treatment (n=20). The aim of this study was to determine the incidence of EC in patients with AEH in University Hospitals of Leicester, UK, and to explore the reasons why patients with AEH opted for conservative management. *Results:* EC was diagnosed in 34.4% of patients with AEH managed by primary surgery. Moreover, the incidence of EC in patients with AEH managed conservatively was 25%. The main reason for opting for conservative management was that patients were unfit for surgery when assessed in the high-risk Anaesthetic Clinic (35%). *Conclusion:* AEH is a pre-malignant lesion that has high risk of EC regardless of the mode of management. Total hysterectomy is the safest first line of treatment in AEH due to the high risk of concurrent EC and progression to EC. Currently, there is no reliable follow-up intervention to distinguish between concurrent EC and progression of AEH.

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**Key Words:** Endometrial cancer, atypical endometrial hyperplasia, mode of management.

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*Adequate discussion and counselling are essential when discussing conservative management for women with complex AEH. Patients should be counselled regarding the high risk of developing concurrent EC and risk of progression to EC.*

Endometrial hyperplasia (EH) is defined as an irregular proliferation of the endometrial glands leading to increase in the gland to stroma ratio in contrast to proliferative endometrium. It is divided into two types based on the presence or absence of cytological atypia. Moreover, it is also classified into simple, or complex based on the extent of architectural abnormality (1). Atypical endometrial hyperplasia (AEH) is considered a pre-malignant lesion or intraepithelial neoplasia (2).

Endometrial cancer (EC) is the sixth most common malignancy worldwide (3). It is considered the most prevalent gynaecological carcinoma in the Western world and EH is its leading risk factor (3).

Risk factors of EH include age, obesity, hypertension, diabetes mellitus, polycystic ovarian syndrome, nulliparity, early menarche and late menopause. Moreover, risk factors include unopposed oestrogen therapy, tamoxifen therapy, failure to ovulate, and family history of hereditary nonpolyposis colorectal cancer (4).

Definitive diagnosis is made by biopsy of the endometrium. Management of AEH is either medical or surgical. The first line of treatment for AEH is total hysterectomy with or without bilateral salpingo-oophorectomy. If fertility is required or surgery is contraindicated, then assessment of the risk factors should be made followed by observing and using Mirena intrauterine system as the first line of treatment. The second line of treatment is oral progestogens. After that, follow-up is recommended every 3 months by taking an endometrial biopsy and the management should be reviewed accordingly (5).

Current Royal College of Obstetricians and Gynaecologists guidelines advise that patients with AEH who will be managed conservatively should undergo a follow-up endometrial biopsy every 3 months. Endometrial biopsy-based follow-up should continue until two successive negative biopsies are found (6). If the endometrial biopsy reveals EC in the first 3 months of

diagnosis of AEH, then it is considered concurrent EC. It is well established that the rate of concurrent EC associated with AEH is high, ranging from 30-50%, due to insufficient sampling or diagnosis by pathologists (7-9).

The main objective of this study was to determine whether the risk of EC is affected by the mode of management of AEH and explore reasons for conservative management.

## Patients and Methods

**Patients.** A retrospective cohort study was conducted. Data for 169 patients with AEH were collected retrospectively using Integrated Clinical Environment software at the University Hospitals of Leicester which contains patients' investigations and letters. Patients' notes were retrieved from 01/01/2015 to 01/01/2020 and were identified using data from cancer centre and histopathology department. Five patients were excluded as their data was incomplete due to being treated privately or abroad. Forty-five patients were found to have either suspicious or confirmed EC with AEH on the initial histopathology results and were excluded from the study.

One hundred and nineteen patients were recruited for the study. Patients were divided into two groups according to the management of AEH: One group underwent primary surgery (n=99), and the second group underwent conservative (medical) management (n=20). Primary surgery included robotic hysterectomy with bilateral salpingo-oophorectomy, robotic hysterectomy with bilateral salpingectomy, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and total abdominal hysterectomy with bilateral salpingo-oophorectomy. Conservative management included levonorgestrel-releasing intrauterine system (Mirena) and oral progestogens.

Patients were included when they met the inclusion criteria. Inclusion criteria were females having a confirmed diagnosis of AEH. Patients declining to have surgery and opting for conservative management were included in the study. Treatment was conservative if the patient received treatment for more than 3 months prior to hysterectomy. Women with suspicion of EC were excluded from the study.

Our data registry included the following: Age, body mass index, diagnostic circumstances, menopausal status, presence of hypertension, presence of diabetes mellitus, history of breast cancer, family history of EH, EC, and colorectal carcinoma. Moreover, ultrasound results, magnetic resonance imaging results, patient-initiated follow-up, follow-up, discharge, death rates, and final histopathology results were included in the data collection.

EC was considered concurrent when diagnosed within a period of 3 months from the diagnosis of AEH. On the other hand, diagnosis of EC after 3 months from the diagnosis of AEH was considered disease progression.

Ethical approval was sought from the Research and Innovation Committee at the University Hospitals of Leicester; however, approval was not required as the study was retrospective.

**Patient management.** Management of AEH was divided into either conservative (medical) or surgical (hysterectomy). The first line of treatment for AEH was total hysterectomy with or without bilateral salpingo-oophorectomy. However, if fertility preservation was needed or the patient was unfit for surgery, then patient counselling was performed with risk factors assessment. Conservative treatment can then be recommended in the form of levonorgestrel-releasing

intrauterine system or oral progestogens. Follow up was done after 3 months by taking an endometrial biopsy and the management was reviewed accordingly.

**Statistical analysis.** Data was fed to the computer and analysed using IBM SPSS software package version 20.0 (IBM Corp., Armonk, NY, USA). Qualitative data were described using number and percentage. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range. Significance of the obtained results was judged at the 5% level.

Chi-square test was used for categorical variables; to compare between the two groups. Fisher's exact test or Monte Carlo was used for correction of chi-square when more than 20% of the cells had expected count less than 5. Student's *t*-test was used to compare normally distributed quantitative variables between the two groups. Mann-Whitney test was used to compare abnormally distributed quantitative variables between the two groups.

## Results

**Patient characteristics.** One hundred and nineteen patients diagnosed with AEH by endometrial biopsy during hysteroscopy were included in the study. Patients were divided into two groups according to the management of AEH: Conservative (n=20) and surgical (n=99).

The patients' demographic characteristics were compared between the two groups (Table I). There was no significant difference between the two groups regarding the age ( $p=0.467$ ), BMI ( $p=0.267$ ), menopausal status ( $p=0.063$ ), history of hypertension ( $p=0.641$ ), history of breast cancer ( $p=0.99$ ), and family history of EH, cancer or colorectal carcinoma ( $p=0.460$ ). Presenting complaints were significantly different between the two groups ( $p=0.005$ ): the proportion of patients presenting with postmenopausal bleeding was significantly higher in patients treated conservatively for AEH, while the proportion presenting with heavy menstrual bleeding was significantly higher in patients treated by surgery.

**Patient investigations.** It was found that there was no significant difference between the endometrial thickness on ultrasound between the two groups ( $p=0.045$ ). In contrast, there was a statistical difference in the number of patients undergoing MRI between the study groups (Table II), with a significantly higher number of patients treated surgically undergoing MRI as compared to the patients treated conservatively ( $p=0.002$ ).

**Modalities of treatment.** In patients who underwent primary surgery, the laparoscopic approach was used in 86% of AEH patients treated with primary surgery: 49.5% robotic hysterectomy with bilateral salpingo-oophorectomy, 34.3% total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and 2.0% robotic hysterectomy with bilateral salpingectomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in 14.1% of patients managed by

Table I. Comparison of patient characteristics according to the management of atypical endometrial hyperplasia.

Variable	Surgical (n=99)	Conservative (n=20)	p-Value
Age, years			
Min.-Max.	36.0-82.0	25.0-88.0	0.467
Mean±SD	59.43±10.73	56.20±18.94	
Median	58.0	58.0	
BMI, kg/m <sup>2</sup>			
Min.-Max.	22.0-60.0	22.0-60.0	0.267
Mean±SD	37.58±7.72	39.80±9.47	
Median	38.0	37.0	
Presenting symptom, n (%)			
PMB	63 (63.6%)	17 (85%)	
HMB	34 (34.4%)	1 (5%)	<b>0.005</b>
Other	2 (2%)	2 (10%)	
Post menopausal, n (%)			
Yes	63 (63.6%)	17 (85%)	0.063
No	36 (36.4%)	3 (15%)	
Hypertension, n (%)			
Yes	39 (39.4%)	9 (45%)	0.641
No	60 (60.6%)	11 (55%)	
Diabetes mellitus, n (%)			
Yes	15 (15.2%)	11 (55%)	<b>&lt;0.001</b>
No	84 (84.8%)	9 (45%)	
History of breast cancer, n (%)			
Yes	9 (9.1%)	2 (10%)	0.99
No	90 (90.1%)	18 (90%)	
Family history of EH/cancer/colorectal carcinoma, n (%)			
Yes	13 (13.1%)	1 (5%)	0.460
No	86 (86.9%)	19 (95%)	

SD: Standard deviation; BMI: body mass index; EH: endometrial hyperplasia; HMB: heavy menstrual bleeding; PMB: postmenopausal bleeding. Statistically significant p-values are shown in bold.

primary surgery. Patients managed conservatively were managed by progestogens: 80% had levonorgestrel-releasing intrauterine system (Mirena) and 20% used oral progestogens.

**Follow-up and outcome.** No statistical difference was noted in the number of patients that had patient-initiated follow-up between the two study groups (p=0.761). A significantly higher proportion of patients were followed-up after conservative management compared with the surgical group (p<0.001). Moreover, the number of patients that were discharged was significantly higher in those managed by primary surgery as compared to those managed conservatively (p<0.001). The number of patients who died was significantly higher in those treated conservatively (p=0.015) (Table III).

Patients with AEH managed by primary surgery were found to have co-existing EC in 34.3% (diagnosed within 3 months): 97% were found to have endometrioid EC and 3% were found to have clear-cell EC. On the other hand, AEH managed conservatively was found to progress to EC in 25% of patients

Table II. Comparison of ultrasound and magnetic resonance imaging (MRI) investigations according to the management of atypical endometrial hyperplasia.

Variable	Surgical (n=99), n (%)	Conservative (n=20), n (%)	p-Value
Ultrasound			
<4 mm	2 (2%)	1 (5%)	<b>0.045</b>
≥4 mm	94 (94.9%)	16 (80%)	
Not done	3 (3%)	3 (15%)	
MRI			
Yes	89 (89.9%)	12 (60%)	<b>0.002</b>
No	10 (10.1%)	8 (40%)	

MRI: Magnetic resonance imaging. Statistically significant p-values are shown in bold.

Table III. Comparison between outcomes according to the management of atypical endometrial hyperplasia.

Variables	Surgery (n=99), n (%)	Conservative (n=20), n (%)	p-Value
PIFU			
Yes	20 (20.2%)	3 (15%)	0.761
No	79 (79.8%)	17(85%)	
FU			
Yes	18 (18.2%)	12 (60%)	<b>&lt;0.001</b>
No	81 (81.8%)	8 (40%)	
Discharge			
Yes	58 (58.6%)	1 (5%)	<b>&lt;0.001</b>
No	41 (41.4%)	19 (95%)	
Died			
Yes	3 (3%)	4 (20)	<b>0.015</b>
No	96 (97%)	16 (80%)	

FU: Follow-up; PIFU: patient-initiated follow-up. Statistically significant p-values are shown in bold.

Table IV. Comparison between the final histopathology according to the management of atypical endometrial hyperplasia.

Variable	Surgery (n=99), n (%)	Conservative (n=20), n (%)	p-Value
No AEH	14 (14.1%)	15 (75%)	<b>&lt;0.001</b>
EH without atypia	13 (1.31%)	0	0.122
AEH	38 (38.4%)	0	<b>0.001</b>
Stage 1A endometrioid EC	31 (31.3%)	5 (25%)	0.575
Stage endometrioid 1B EC	1 (1.0%)	0	>0.99
Stage 1A clear-cell EC	1 (1.0%)	0	>0.99
Stage 2 EC	1 (1.0%)	0	>0.99

EC: Endometrial carcinoma. Statistically significant p-values are shown in bold.

within 5 years (Table IV). There was no statistically significant difference in the risk of EC in patients with AEH treated by primary surgery as compared to those treated conservatively.

## Discussion

Future risk of EC has always been of great concern, especially in patients with AEH. It is well established that EC incidence has increased dramatically over the past decade (10). In some countries, EC has been diagnosed in more than 50% of patients diagnosed with AEH who were advised to be treated in gynaecology centres (11). In developed countries, it is the most common gynaecological cancer, with 5-year overall survival ranging between 74 to 94% (12). Hysterectomy, old age, obesity, diabetes mellitus and increased endometrial thickness were found to be strong predictors for concurrent EC (13, 14).

We studied the risk of EC in patients with AEH. Our study is one of the few studies to compare the risk of EC in patients with AEH according to the mode of management: primary surgery and conservative. The primary aim of the study was to observe how the risk varies according to the mode of management of the patients.

The results revealed that the risk of EC was high for both arms of the study and the highest EC risk was found in the group of patients with AEH managed surgically by primary hysterectomy. Hence, the conservative management had a lower probability of developing EC, but it is difficult to rule out concurrent EC. No statistical difference was noted in the EC risk for both groups of study.

A systematic review and meta-analysis was published by Doherty *et al.* in 2020 aiming to assess the coexisting and future incidence of EC in women diagnosed with EH (15). The analysis noted that it was unclear in most articles whether a time distinction was made to differentiate between coexisting EC and the progression to EC in patients with AEH. It revealed the future risk of developing EC to be 3% in patients with EH without atypia; however, the future risk increases to 8% in patients with AEH (15). The prevalence of EC in patients with EH without atypia was nearly 32%. However, the prevalence of EC in patients with AEH ranged between 5.9% and 53.1% in 15 different studies (15).

In another retrospective study, it was concluded that the risk of EC in patients with AEH treated by primary hysterectomy was 37% in 36 months as compared to 26% in patients treated through fertility-sparing management. The study showed no statistical difference in the risk of EC in patients with AEH managed by primary hysterectomy and by fertility-sparing methods (16).

It was important to explore why patients underwent conservative measures as management of AEH. We were interested to find if it was to preserve fertility or if surgical management was not an option. In our study, patients were treated conservatively as 35% were unfit for surgery as assessed

in the high-risk Anesthetic Clinic and 25% of the patients were fit for surgery but declined the procedure. Furthermore, 20% of the patients were advised to lose weight before commencing surgery, 15% wished to preserve their fertility, and 5% were transferred to another hospital as they moved to another city.

The three patients that underwent conservative management to preserve their fertility have not yet become pregnant. Previous research established that in patients with AEH, assisted reproduction should commence promptly after conservative management as AEH has high rates of recurrence and progression to EC (17, 18). Even in severe AEH, it was established that assisted reproduction can be a good management option (19).

There was a total of seven deaths amongst the participants during the 5 years of the study: Three from the surgically managed group and four from the conservatively managed group. The causes of death were explored in both groups. In the three patients managed surgically the causes of deaths were metastatic pancreatic cancer, subarachnoid haemorrhage and von Willebrand disease with bilateral pleural effusion; in patients managed conservatively, two died from metastatic colon cancer, one from atrial fibrillation and infective endocarditis, and one from hypertensive disease.

There was no statistically significant difference in the mean age of the two groups ( $p=0.467$ ). This was one of the main strengths of the study as age is one of the prognostic factors for EC. Having two groups of the study with no significant difference in age ensured a more accurate outcome of the mode of management and no associated bias. Indeed, it might be expected that patients with younger age opt for conservative management to preserve fertility and that AEH might be diagnosed during infertility workup (20). However, another study involving 824 patients with AEH, concluded that the patient's age is directly correlated to the incidence of EC (21).

There are some limitations to our study. It was a retrospective study. The number of patients receiving conservative management was relatively lower ( $n=20$ ) than those undergoing primary hysterectomy ( $n=99$ ). Another limitation is that we did not include patients with simple EH as a control.

We believe that studies of patients with atypical and non-atypical hyperplasia are essential to estimate the probability of concurrent and future EC. Hence, a high-risk group can be targeted for preventative measures. Furthermore, more research should be carried out to improve the differentiation between AEH and EC.

## Conflicts of Interest

None.

## Authors' Contributions

AB was involved in conceptualization, validation, formal analysis, investigation, data curation and writing of the article. AI was

involved in conceptualisation, reviewing and editing of the article. SC was involved in conceptualisation, reviewing and editing of the article. QD was involved in conceptualisation, reviewing, and editing the article. All Authors read and approved the final article.

## Acknowledgements

The Authors thank all the gynaecology consultants at the University Hospitals of Leicester for allowing us to take details of their patients and their management plans. The Authors would also like to thank Anju Mathews, a clinical fellow in the Obstetrics and Gynaecology Department, for assisting in the data collection.

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Received June 13, 2022

Revised June 26, 2022

Accepted July 13, 2022