Endometrial cancer after endometrial ablation: a systematic review

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ABSTRACT

Objective To investigate whether a previously performed endometrial ablation is associated with the development and diagnosis of endometrial cancer.

Methods First, a systematic review was performed of the articles reporting the incidence of endometrial cancer in patients treated with endometrial ablation. Second, a systematic review was performed to identify all individual cases of endometrial cancer after ablation to evaluate presenting symptoms, diagnostic work-up, potential risk factors, and the type and stage of the endometrial cancer. A systematic search was performed, using Medline, EMBASE, and the Cochrane Library databases, from inception through February 24, 2022.

Results Based on 11 included studies, the incidence of endometrial cancer in a population of 29 102 patients with a prior endometrial ablation ranged from 0.0% to 1.6%. A total of 38 cases of endometrial cancer after ablation were identified. In 71% of cases (17 of 24 cases), vaginal bleeding was the first presenting symptom. With transvaginal ultrasound it was possible to identify and measure the endometrial thickness in eight cases. Endometrium sampling was successful in 16 of 18 described cases (89%). In 18 of 20 cases (90%) pathologic examination showed early-stage endometrioid adenocarcinoma (International Federation of Gynecology and Obstetrics stage I).

Conclusion Previous endometrial ablation is not associated with the development of endometrial cancer. Diagnostic work-up is not impeded by previous endometrial ablation. In addition, endometrial cancers after endometrial ablation are not detected at an advanced stage.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is unclear whether a previously performed endometrial ablation has a negative effect on the diagnostic work-up and development of endometrial cancer as literature on the correlation between endometrial cancer after ablation is limited.

WHAT THIS STUDY ADDS

⇒ According to the results of this study, treatment with endometrial ablation does not appear to increase the risk of endometrial cancer or delay its diagnosis. Instead, endometrial ablation indicates a reduced risk of endometrial carcinoma. Additionally, endometrial sampling appears to be an effective diagnostic method after endometrial ablation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may increase awareness of the correlation between endometrial ablation and endometrial carcinoma, encouraging more research to be conducted. Therefore, these findings may be helpful in counseling patients considering endometrial ablation.

INTRODUCTION

Endometrial ablation as a treatment option for heavy menstrual bleeding has gained popularity since techniques have improved over the last two decades.[1 2] However, due to amenorrheic menstrual patterns and the development of intrauterine and intracervical adhesions, questions have risen about difficulties of diagnosing endometrial pathology after ablation. There is a particular concern that diagnosis of endometrial cancer may be missed or recognized too late, because post-menopausal bleeding could be absent or delayed.[3] Endometrial cancer is the most common gynecologic malignancy worldwide, with a yearly increasing mean incidence of 3.1% lifetime risk in the general population in 2021.[4] More than 90% of the patients present with post-menopausal bleeding or heavy or irregular menstrual bleeding.[5] Due to the presentation of unexpected vaginal bleeding, endometrial cancer is diagnosed at an early stage of disease in around 75% of cases, resulting in high survival rates.[6 7]

Transvaginal ultrasonography is mostly used as diagnostic tool to visualize the endometrium thickness and regularity. Generally, when the total endometrium thickness is more than 3 to 4 mm or the endometrial profile is of irregular aspect, the Royal College of Obstetricians and Gynecologists guideline recommends endometrium sampling to examine the microscopic aspect of the endometrium.[8–10] It is unclear whether a previously performed endometrial ablation has a negative effect on the diagnostic work-up of endometrial cancer as literature on the correlation between endometrial cancer after ablation is limited.[11 12] A potential problem could be the decrease in sensitivity of ultrasound features after ablation because of changes in the endometrium and difficulties in recognition of the endometrial thickness.

Furthermore, difficulties in endometrial sampling due to intrauterine adhesions might be expected.[3 13–16]

The aim of this systematic review is to investigate whether a previous performed endometrial ablation is associated with the development and diagnosis of endometrial cancer.

This review concentrated on two objectives. First, a systematic review of studies describing the incidence of endometrial cancer after endometrial ablation. Second, an evaluation of all cases as described in the literature on endometrial cancer after ablation to evaluate first symptoms, diagnostic work-up, potential risk factors, and the type and stage of endometrial cancer.

METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were used to report our systematic review.[17] The protocol was registered in PROSPERO, international prospective register of systematic reviews (ID: CRD42020175973).[18] In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team for the purposes of additional data analysis or for reproducibility of this study.

Database Search

A broad systematic search was performed, to answer both research questions, using Medline, EMBASE, and the Cochrane Library databases from inception through February 24, 2022, aided by an information and database analyst. Searching with Medline keywords: endometrial ablation techniques, endometrial neoplasms/carcinoma/cancer/tumor, cancer/carcinoma of the endometrium or endometrium carcinoma. A complete overview of the search can be found in online supplemental file 1.

Incidence of Endometrial Cancer after Endometrial Ablation

Eligibility Criteria

For the systematic review all original articles reporting the incidence of endometrial cancer in a population of patients with a prior endometrial ablation were included. No distinction between endometrial ablation techniques was made. Exclusion criteria were publications in which endometrial ablation was performed for indications other than heavy menstrual bleeding, and articles or cases were excluded if endometrial cancer was diagnosed before or during the ablation. Publications were also excluded if no full text was available, or the article could not be translated to English.

Outcome

The primary outcome was to establish the incidence of endometrial cancer in patients previously treated with endometrial ablation for heavy menstrual bleeding.

Selection of Eligible Articles

All publications were imported in the program Rayyan QCRI, and duplicates were removed.[19] Two independent reviewers (TJO and MRDK) assessed each abstract and selected full text articles matching the inclusion and exclusion criteria. Any disagreement was solved by discussion or by means of a third reviewer (KMCC).

Data Extraction

The data were systematically collected in a data extraction sheet with article information (name of author and year of publication), study design, ablation techniques, range or mean/median follow-up, number of participants, and number of cases of endometrial cancer identified.

Statistical Analysis

We used descriptive statistics to report data on incidence of endometrial cancer in patients with a prior endometrial ablation.

Risk of Bias Assessment

The risk of bias for the included cohort studies was assessed using the ROBINS-I tool. For randomized controlled trials, the risk of bias was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[20 21] Both were assessed by two individual reviewers (TJO and MRDK). The studies were rated low risk of bias, moderate risk of bias, high risk of bias, or unclear. Any disagreement on the classification of risk of bias was resolved by discussion or by means of a third reviewer (KMCC).

Reported Case Studies

Eligibility Criteria

Articles describing individual cases of endometrial cancer after endometrial ablation were included. Exclusion criteria were the same as described above.

Outcomes and Data Extraction

We reviewed all cases reporting endometrial cancer in patients treated with endometrial ablation for heavy menstrual bleeding and reviewed data on presenting symptoms, the diagnostic work-up, and type and stage of cancer. Also, article information (name of author and year of publication), potential risk factors, ablation technique, age at time of endometrial cancer diagnosis, time from ablation to cancer diagnosis, and type of treatment were collected.

RESULTS

Included Studies

Our literature search yielded in total 890 publications from Medline database (n=184), Cochrane Library (n=4) and EMBASE database (n=702). After duplicates were removed, 734 publications were left for assessment. Eventually, 11 articles were included in the systematic review on incidence of endometrial cancer after endometrial ablation; nine retrospective studies, one prospective cohort study, and one randomized controlled trial.[3 13–16 22–27] Twenty-four articles were included describing a total of 38 individual cases of endometrial cancer after ablation.[3 11 13–15 22–25 27–41] The flow diagram for study selection is shown in Figure 1.

Incidence of Endometrial Cancer after Endometrial Ablation

According to the incidence data from 10 cohort studies and one randomized controlled trial, 29102 patients after endometrial ablation were followed up for a period until 25 years after ablation (Table 1).[3 13–16 22–27] The incidence of endometrial cancer after endometrial ablation varied from 0.0% to 1.6%.

Reported Case studies

From our extensive search, 24 articles were included describing single or multiple cases of endometrial cancer after ablation.[3 11 13–15 22–25 27–41] In total 38 cases were described. A summary

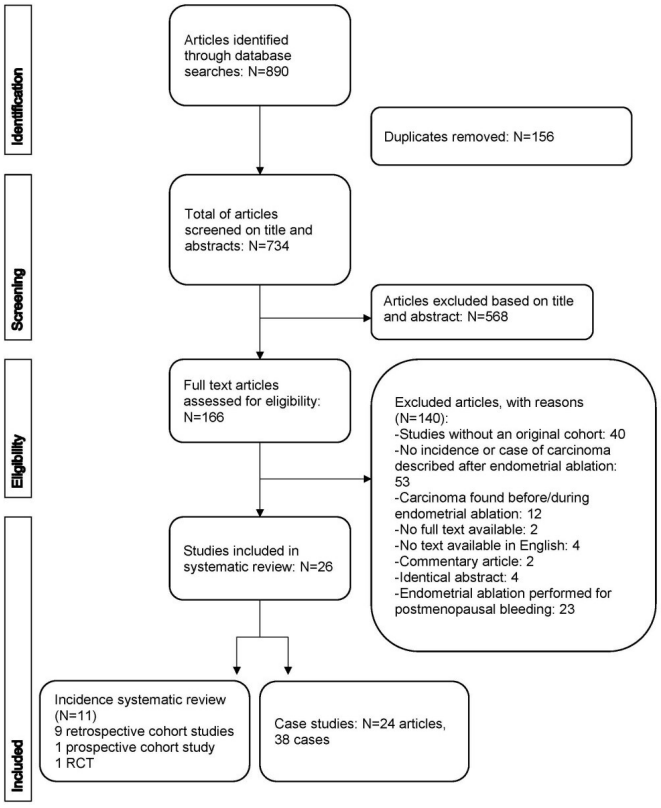

Figure 1 Flow diagram for study selection.

of these included cases is shown in Table 2, and a detailed elaboration of the cases is provided in online supplemental file 2.

In 17 of 24 cases (71%) vaginal bleeding was the mean reason for patients to consult the gynecologist and five patients (21%) presented with pelvic pain. The discovery of two cases (8%) of asymptomatic endometrial adenocarcinoma was unexpected. The first patient had a hysterectomy as part of prolapse surgery, and the other had an ultrasound as part of a study by Morelli et al investigating ultrasound images in patients who have had endometrial ablation.[15] In nine cases the assessment of the endometrium was performed using transvaginal ultrasonography. In eight cases a thickened endometrium more than 7 mm, or irregular endometrium/myometrium, was described, with consequently a biopsy. In the case of Morelli et al,[15] the ultrasound image showed an intracavitary collection of fluid, thus hysteroscopy and biopsy were performed.

Endometrial sampling was performed using pipelle or hysteroscopic biopsy in 18 of the 21 cases and was successful in 16 (89%) cases. In three cases endometrial biopsy initially failed due to intrauterine adhesions. In one of these cases, biopsy was eventually successful using a smaller hysteroscope and hysteroscopic surgery with partial removal of intracervical and intrauterine adhesions. In the remaining two cases a hysterectomy was performed to confirm the diagnosis.

The type and stage of endometrial cancer is known for 53% of the cases (20 cases). At the time of diagnosis 90% (n=18) of cases showed stage I endometrioid-type adenocarcinoma according to the International Federation of Gynecology and Obstetrics (FIGO), and one case showed FIGO stage II/III endometrial adenocarcinoma. In one case histology showed a villoglandular adenocarcinoma. In 15 cases (71%) pathology showed well-differentiated endometrial adenocarcinoma and in six cases (29%) pathology revealed moderately or poorly differentiated endometrial adenocarcinoma.

DISCUSSION

Summary of Main Results

Based on 11 studies, the incidence of endometrial cancer among patients with a history of endometrial ablation varies from 0.0% to 1.6%. Thirty-eight cases of endometrial cancer after ablation are described in the literature. In 71% of the cases, vaginal bleeding was the presenting symptom of the disease. Endometrium sampling was successful in 89% of cases, and in 90% of cases pathologic examination showed early-stage endometrioid adenocarcinoma (FIGO stage I).

Table 1 Incidence of endometrial cancer after endometrial ablation (n=11)

Author (year)	Study design	Population (N)	Number of EC cases (N)	Follow-up time in years, mean*/median† (range)	Incidence (%)
Bhattacharya et al 2011[22]	Retrospective cohort study	11 299	2	6.2† (2.7–10.8)	0.02
Cooper *et al* 2005[23]	Randomized controlled trial	263	1	NA (5.2–7)	0.38
Dood *et al* 2014[13]	Retrospective cohort study	4776	3	5.5† (IQR 3.2–8)	0.06
Gaia *et al* 2007[24]	Retrospective cohort study	3769	1	NA (0–11)	0.03
Kalampokas *et al* 2018[14]	Retrospective observational study	901	2	NA[18–25]	0.22
Krogh *et al* 2009[25]	Retrospective cohort study	367	3	11.1* (8.1–14.6)	0.82
Morelli *et al* 2015[15]	Retrospective observational study	63	1	NA (0–14)	1.59
Neuwirth *et al* 2004[3]	Retrospective cohort study	466	2	NA[6–24]	0.43
Panoskaltsis *et al* 2002[26]	Prospective observational study	193	0	6† (IQR 4–7)	0.0
Singh et al 2016[16]	Retrospective observational study	1521	0	10†[2–17]	0.0
Soini *et al* 2017[27]	Retrospective cohort study	5484	3	7.3* (0–18)	0.05

*Mean follow-up.
†Median follow-up.
EC, endometrial carcinoma; IQR, interquartile range.

Table 2 Summary of endometrial cancer cases after endometrial ablation (n=38)

	Number of endometrial carcinoma cases, N	Percentage of endometrial carcinoma cases/total (%)
Total cases	38	
Ablation methods	32	
Resectoscope	9	28
Roller-ball	5	16
(not specified) Hysteroscopic	6	19
Endometrial ablation		
(not specified) Non-hysteroscopic	1	3
Endometrial ablation		
Thermal balloon	4	13
Radio-frequent endometrial ablation	4	13
Mix of methods	3	9
Risk factors	20*	*
(Morbid) obesity	13	65
Diabetes mellitus	4	20
Hypertension	6	30
History of cancer	2	10
Nulliparity	1	5
Estrogen/hormone replacement therapy	2	10
Polycystic ovary syndrome	1	5
None	4	20
Symptoms	24*	*
Vaginal bleeding	17	71
Pelvic pain	5	21
Asymptomatic	2	8
Diagnostic tools	21*	*
Pelvic examination	2	10
Ultrasound	9	43
Hysteroscopy	9	43
Hydrosonography	1	5
Successful endometrial biopsy	16	76
Unsuccessful endometrial biopsy	2	10
Cervix cytology	2	10
CT scan	1	5
Type and stage of cancer (FIGO)	20	
Endometrioid adenocarcinoma stage I	18	90
Endometrioid adenocarcinoma stage II/III	1	5
Endometrioid adenocarcinoma stage III	0	0
Villoglandular adenocarcinoma	1	5

*The sum of these percentages is not 100%, due to multi possible answers.
FIGO, International Federation of Gynecology and Obstetrics.

Results in the Context of Published Literature

Incidence of Endometrial Carcinoma after Endometrial Ablation

Based on the results of this review the incidence of endometrial cancer varies from 0.0% to 1.6% in patients with a prior endometrial ablation. The lifetime incidence of endometrial carcinoma in the general population is 3.1%.[4] The available literature is limited and nine out of 11 included studies had a follow-up period of less than 15 years. As most patients receive endometrial ablation when they are pre-menopausal or peri-menopausal, a follow-up period of at least 15 to 20 years is necessary to detect the majority of endometrial cancers, since the peak incidence of endometrial cancer in the general population is at around 61 years old.[42–44] The prospective study of Kalampokas et al[14] studied patients (n=901) with endometrial ablation with a follow-up period of 18 to 25 years after ablation and found an incidence of endometrial carcinoma of 0.2%.[14] Also, in the study of Neuwirth et al,[3] with a follow-up duration of up to 24 years, an incidence of 0.4% endometrial cancer after ablation was found.[3] These results still confirm our finding of no increased risk for the development of endometrial cancer after ablation.

Nevertheless, confounding is a problem in the comparison of endometrial cancer between patients treated for heavy menstrual bleeding and the general population. Hypothetically, these patients have an increased risk of developing endometrial cancer since anovulatory bleeding and hyperplasia (common causes of heavy menstrual bleeding) coincide with obesity, which is associated with an increased risk of endometrial cancer. However, clear evidence from literature is lacking. In the study of Dood et al, confounding is partly addressed by comparing patients with heavy menstrual bleeding treated with endometrial ablation and patients receiving medical management. No increased risk of endometrial carcinoma was found, with 0.06% in the endometrial ablation group versus 0.26% in the medical management group. However, the median follow-up duration in both groups was relatively short, 5.5 and 4 years, respectively.[13] More long-term data are needed.

Reported Case Studies of Endometrial Carcinoma after Endometrial Ablation

There are only limited data available on endometrial cancer after endometrial ablation, as we identified only 38 cases in our systematic literature search. It is likely that there is under-reporting of the cases. Moreover, in 11 out of 38 cases, information on time between ablation and cancer diagnosis was limited .

Unexpected vaginal bleeding is of substantial importance to diagnose endometrial cancer at an early stage. In this review, 74% of the patients presented with unexpected vaginal bleeding after treatment with endometrial ablation, which is lower than 90% in the general population.[5] A total of 22% of patients presented with pelvic pain. All cases were diagnosed at early stage of disease. The symptoms at presentation of endometrial cancer appear to be consistent with those of the general population. Transvaginal ultrasonography after endometrial ablation can be inconclusive, because of the total destruction of the endometrial basic layer, which impairs endometrial growth.[45 46] In this review the findings of transvaginal sonography are described in only eight cases. However, in a study of Arora et al, 71% of patients treated with endometrial ablation appeared to have a measurable endometrium on transvaginal sonography.[31]

Moreover, there are questions on the accessibility of the uterine cavity after treatment with endometrial ablation due to the presence of intrauterine adhesions, resulting in difficult endometrial sampling.[9 12 37] However, the results of this review do not confirm a reduced success rate of endometrial sampling, as 89% of the cases were diagnosed with endometrial sampling using pipelle and/or hysteroscopic biopsies. The study of Arora confirms these results, as in their study endometrial biopsies failed in only 8% (12/153) of the cases, and a hysteroscopic sampling succeeded in 94% of cases.[31] In addition, MacMahon et al (2018) described six cases in which access to the uterine cavity was difficult. Nevertheless, they all succeeded in obtaining a biopsy by hysteroscopy. All pathological findings were detected.[37]

Ninety per cent of cases were diagnosed as FIGO stage I endometrioid adenocarcinoma compared with 75% in the general population.[6 7] This suggests that diagnosing endometrial cancer does not seem to be delayed in patients with endometrial ablation.

Strengths and weaknesses

This is the first systematic review reporting all described endometrial cancers in patients treated with endometrial ablation for heavy menstrual bleeding. An extensive search of the literature was performed to detect all reported cases on endometrial cancer in patients who were treated with endometrial ablation for the indication of heavy menstrual bleeding. The latest review on this subject of Bardawil et al[12] found 37 cases, including six cases of patients treated with endometrial ablation as treatment for postmenopausal bleeding, four cases of patients diagnosed with endometrial cancer at the time of ablation, and two cases that did not contain any clinical information. We have excluded those cases in this review and thus found 13 new cases, providing a more representative impression of the cohort patients with endometrial carcinoma after ablation.

Limitations of this systematic review are the small number of available prospective studies and randomized controlled trials, causing a risk of publication and selection bias. The use of different types of ablation techniques in the included studies could possibly result in bias of the outcome. Also, due to the wide range of follow-up between the studies (0 to 25 years), calculation of the mean incidence cannot be expressed for a specific time, and a lifetime incidence cannot be calculated. The data could not be pooled, because of various methodological issues—namely,variation in population sizes, different types of study design, and most importantly, the differing follow-up times among studies, which affect the occurrence of cancer.

All 11 included studies in the systematic review scored a moderate to high risk of bias. Specifically, bias due to confounding was of risk for our primary outcome measure due to the absence of information on risk factors for endometrial carcinoma or when endometrial ablation was not specified as treatment for heavy menstrual bleeding. In addition, three studies scored a serious risk of bias in participant selection due to an unrepresentative group of patients included in the analyses. The bias table can be found in online supplemental file 3. Moreover, 11 of the 38 cases found in literature (28.9%) had missing data, which further increased the risk of (reporting and selection) bias.

Implications for Practice and Future Research

According to our results, treatment with endometrial ablation does not appear to increase the risk of endometrial cancer. Instead, these results suggest a reduced risk of endometrial carcinoma. Some studies argue that endometrial ablation may be a protective factor for developing endometrial cancer.[16 47] Hypothetically a reduction in the amount of the endometrium tissue caused by endometrial destruction would decrease the chance of developing a malignancy. However, owing to limited available data, until now evidence to support this hypothesis is not sufficiently strong. Research with proper control groups (patients with heavy menstrual bleeding) after endometrial ablation including long term follow-up is recommended to improve our understanding of the relation between endometrial ablation and the development of endometrial cancer.

CONCLUSIONS

Based on 11 cohort studies, we can conclude that the incidence of endometrial cancer does not seem to increase in patients with a history of endometrial ablation. There appears to be no delay in the diagnosis of endometrial cancer after endometrial ablation, as diagnostic management with endometrial sampling does not seem to be a barrier after ablation. In addition, endometrial cancers after endometrial ablation do not appear to be detected at a more advanced stage of the disease.

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Supplementary file 1. Search Strategy

Search Medline 24-02-2022

("Endometrial Ablation Techniques"[MeSH Terms] OR ("endometri*"[Title/Abstract] AND "ablat*"[Title/Abstract])) AND ("Endometrial Neoplasms"[MeSH Terms] OR "endometrial neoplasm*"[Title/Abstract] OR "endometrial carcinoma*"[Title/Abstract] OR "endometrial cancer*"[Title/Abstract] OR "endometrium cancer*"[Title/Abstract] OR "endometrial tumor*"[Title/Abstract] OR "endometrial tumour*"[Title/Abstract] OR "endometrium tumor*"[Title/Abstract] OR "endometrial tumour*"[Title/Abstract] OR "cancer of the endometrium"[Title/Abstract] OR "carcinoma of endometrium"[Title/Abstract] OR "endometrium carcinoma*"[Title/Abstract] OR "cancer of endometrium*"[Title/Abstract])

Embase search 24-02-2022

('endometrium ablation'/exp OR ((endometri* AND ablat*)):ti,ab,kw) AND ('endometrium tumor'/exp OR ('endometrium tumor*' OR 'endometrium tumour*' OR 'endometrial tumor*' OR 'endometrial tumour*' OR 'endometrial neoplasm*' OR 'endometrial carcinoma*' OR 'endometrial cancer*' OR 'endometrium cancer*' OR 'endometrium carcinoma*'):ti,ab,kw)

Cochrane search 24-02-2022

("Endometrial Ablation Techniques"[MeSH Terms] OR ('endometri*' AND 'ablat*')) AND ("Endometrial Neoplasms"[MeSH Terms] OR 'endometrial neoplasm*' OR 'endometrial carcinoma*' OR 'endometrial cancer*' OR 'endometrium cancer*' OR 'endometrial tumor*' OR 'endometrial tumour*' OR 'endometrium tumor*' OR 'endometrial tumour*' OR 'cancer of the endometrium' OR 'carcinoma of endometrium' OR 'endometrium carcinoma*' OR 'cancer of endometrium*')

Supplementary file 2. Cases of endometrial cancer after endometrial ablation (N=38 cases), 24 articles.

Author (year)	Ablation method	Age at cancer diagnosis, year	Risk factors	Symptoms	Diagnostic work-up	Time from ablation to cancer diagnosis	Treatment	Pathological findings after treatment (FIGO stage 1988)
AlHilli et al. (2011)	Radiofrequency ablation	47	Obesity, hypertension	Vaginal bleeding	Ultrasound, hysteroscopy, biopsy	5 years	Hysterectomy + BSO	Stage IA, endometrial adenocarcinoma, grade 1
Areia et al. (2006)	Resectoscope + rollerball	50	Nulliparous	Intense pelvic pain	NA	30 months	Hysterectomy + BSO	Endometrial adenocarcinoma, grade 1
Argall et al. (2016) **1st case**	Thermal balloon + radiofrequency	47	NA	NA	Biopsy	34 months	Hysterectomy	Stage IA, endometrioid adenocarcinoma, grade 1
2nd case	NA	53	NA	NA	Biopsy	5 years	Hysterectomy	Stage IA, endometrioid adenocarcinoma, grade 2
Arora et al. (2020)	NA	NA	NA	NA	Biopsy	NA	Hysterectomy	Endometrial adenocarcinoma, grade 1
Baggish et al. (1995)	Rollerball	52	Morbid obesity, DM, hypertension	Vaginal bleeding	Pap smear with abnormal endometrial cells, CT-scan	6 months	Hysterectomy + BSO and pelvic washings	Stage I, endometrioid adenocarcinoma, grade 1
Bhattacharya et al. (2011) **1st case**	Hysteroscopic endometrial ablation	NA	NA	NA	NA	NA	NA	NA
2nd case	Non hysteroscopic endometrial	NA	NA	NA	NA	NA	NA	NA

	ablation							
Brooks-Carter et al. (2000)	Rollerball	55	Morbid obesity, DM, hypertension	Vaginal bleeding	Biopsy	5 years	Radiation therapy + intrauterine cesium implants	Villoglandular adenocarcinoma
Cooper et al. (2005)	Microwave ablation + resectoscope	NA	NA	NA	NA	NA	NA	NA
Copperman et al. (1993)	Resectoscope	56	Obesity, DM, hypertension, colon cancer	Vaginal bleeding	Biopsy	5 years	Hysterectomy, + BSO, adjuvant radiation	Stage II/III, Endometrium adenocarcinoma, grade 2
Dood et al. (2014) **1st case**	NA	NA	NA	NA	NA	5 months	NA	NA
2nd case	NA	NA	NA	NA	NA	7.6 months	NA	NA
3rd case	NA	NA	NA	NA	NA	3.6 years	NA	NA
Gaia et al. (2007)	Resectoscope	62	Obesity, HRT	Vaginal bleeding	Ultrasound, biopsy	6 years	Hysterectomy + BSO + bilateral pelvic lymphadenectomy + brachytherapy	Stage IC, Endometrioid adenocarcinoma, grade 1
Iqbal et al. (1997)	Resectoscope	53	None	Vaginal bleeding	Hysteroscopy, biopsy	3 years	Hysterectomy + BSO	Stage IB Endometrioid adenocarcinoma, grade 2
Kalampokas et al. (2018)	Resectoscope	66	Obesity	Vaginal bleeding	NA	18 years	NA	Stage IA, endometrioid adenocarcinoma

1st case								
2nd case	Resectoscope	57	None	Vaginal bleeding	NA	18 years	NA	Stage IA, endometrioid adenocarcinoma
Krogh et al. (2009) **1st case**	Resectoscope	NA	NA	NA	NA	NA	NA	NA
2nd case	Resectoscope	NA	NA	NA	NA	NA	NA	NA
3rd case	Resectoscope	NA	NA	NA	NA	NA	NA	NA
Le Marrec et al. (2009)	Thermal balloon	54	Obesity, breast cancer in history	Vaginal bleeding	Hydrosonography, hysteroscopy, biopsy	6 years	Hysterectomy + pelvic lymph node dissection	Stage IA, endometrioid adenocarcinoma, grade 2
MacMahon et al. (2018)	Thermal balloon	54	Obesity	Vaginal bleeding	Ultrasound, Hysteroscopy, biopsy	8 years	Hysterectomy + BSO	NA
Margolis et al. (1995)	Rollerball	58	Hypertension, diabetes, obesity	Stress incontinence and dysuria	Pelvic exam	3 years	Hysterectomy + BSO	Stage IC, Endometrioid adenocarcinoma, grade 1-2
Morelli et al. (2015)	NA	NA	NA	Asymptomatic	Ultrasound, hysteroscopy, biopsy	NA	NA	Stage IA, Endometrioid adenocarcinoma, grade 2
Neuwirth (2004) **1st case**	Hysteroscopic endometrial ablation	NA	NA	NA	NA	2.5 years	NA	Stage I, endometrial cancer, grade 1
2nd case	Hysteroscopic endometrial ablation	NA	NA	NA	NA	NA	NA	NA

Ramey et al. (1994)	Rollerball	39	Obesity, PCOS	Vaginal bleeding	Hysteroscopy, biopsy	9 months	Hysterectomy + BSO, appendectomy, pelvic and para-aortic lymph node dissection + peritoneal washings	Stage IA, endometrioid adenocarcinoma adenocarcinoma, grade 1
Sagiv et al. (2005)	Resectoscope	60	None	Pelvic pain, vaginal bleeding	Ultrasound, failed biopsy	3 years	Hysterectomy + BSO	Stage IC, endometrioid adenocarcinoma, grade 1
Soini et al. (2017) **1st case**	Hysteroscopic endometrial ablation	NA	NA	NA	NA	NA	NA	NA
2nd case	Hysteroscopic endometrial ablation	NA	NA	NA	NA	NA	NA	NA
3rd case	Hysteroscopic endometrial ablation	NA	NA	NA	NA	NA	NA	NA
Wortman et al. (2016)	Radiofrequency endometrial ablation	40	None	Extreme cyclic pelvic pain	Ultrasound, hysteroscopy	2 years	Hysterectomy + BSO, lymphadenectomy	Endometrioid adenocarcinoma, grade 1
Wortman et al. (2017) **1st case**	Radiofrequency endometrial ablation	41	Obesity, DM	Severe pelvic pain	Ultrasound, failed biopsy, CA-125 elevated	7 years	Hysterectomy	Stage IA, Endometrioid adenocarcinoma, grade 1
2nd case	Rollerball	50	Obesity	Vaginal bleeding	Biopsy	17 years	Hysterectomy + BSO, pelvic and para-aortic	Endometrioid adenocarcinoma, grade

							lymph node dissection	3
3rd case	Thermal balloon	55	Hypertension	Vaginal bleeding	Pelvic exam, ultrasound, PAP smear, biopsy	10 years	Hysterectomy + BSO	Stage IA, Endometrioid adenocarcinoma, grade 1
4th case	Thermal balloon	50	Morbid obesity	Vaginal bleeding and pelvic pain	Hysteroscopic biopsy	7 years	Hysterectomy + BSO with peritoneal washings.	Stage IA, Endometrioid adenocarcinoma, grade 1
5th case	Radiofrequency endometrial ablation	55	Unopposed estrogen	Vaginal bleeding	Ultrasound, hysteroscopy, biopsy	6 years	Hysterectomy + BSO + periaortic and pelvic lymphadenectomy	Stage IA, Endometrioid adenocarcinoma, grade 1

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; NA = data not available or not described in article; BSO= bilateral salpingo-oophorectomy; DM=Diabetes Mellitus; HRT = Hormone replacement therapy ; PCOS = Polycystic ovary syndrome

Supplementary file 3: Methodologic quality of included studies (n=11)

Author (year)*	Bias due to confounding	Bias in selection of participants	Bias in clarification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurements of outcome	Bias in selection of the reported result	Overall bias
Bhattacharya et al. (2011)	+	-	-	NI	++	+	++	Serious risk
Dood et al. (2014)	+	+	-	NI	++	+	++	Serious risk
Gaia et al. (2007)	-	-	+	NI	++	+	++	Serious risk
Kalampokas et al. (2018)	++	+	++	NI	++	+	++	Moderate risk
Krogh et al. (2009)	+	++	+	NI	+	+	++	Moderate risk
Morelli et al. (2015)	+	-	+	NI	NI	+	++	Serious risk
Neuwirth et al. (2004)	+	++	++	NI	+	+	++	Moderate risk
Panoskaltsis et al. (2002)	++	++	++	NI	++	+	++	Moderate risk
Singh et al. (2015)	+	++	++	NI	++	+	++	Moderate risk
Soini et al. (2017)	+	+	+	NI	++	+	++	Moderate risk

* Robins-I tool (N=11), ++ =low risk of bias; + = moderate risk; - = serious risk; -- = critical risk; NI = No information

Author (year)**	Bias due to randomization process	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurements of outcome	Bias in selection of the reported result	Overall bias
Cooper et al. (2005)	+	+/-	+	+	+	Some concerns

** RoB-2 tool Risk of bias for randomised controlled trial (N=1), + = low risk of bias, +/- = some concerns, - = high risk of bias, NI = No information