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Clinical Predictive Factors of Response to Treatment in Patients Undergoing Conservative Management of Atypical Endometrial Hyperplasia and Early Endometrial Cancer

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Purpose: Predictive markers of response to conservative treatment of atypical endometrial hyperplasia (AEH) or early endometrial cancer (EEC) are still lacking. We aimed to assess clinical predictive factors of response to conservative treatment of AEH and EEC.

Methods: All patients with AEH or EEC conservatively treated from January 2007 to June 2018 were retrospectively assessed. The associations between 23 clinical factors and outcomes of response to treatment were assessed with standard univariate analyses and multivariate logistic regression (significant p-value <0.05).
The primary outcome was the association of each clinical factor with treatment failure (i.e., no regression or relapse of the disease). Secondary outcomes were the associations of each clinical factor with: (1) no regression, (2) relapse, or (3) pregnancy after treatment.

Results: Forty-three women, 37 (86%) with AEH and 6 (14%) with EEC were included. At univariate analyses, treatment failure was associated with longer menstrual cycle ($p=0.002$), infrequent menstrual bleeding ($p=0.04$), and a diagnosis of EEC instead of AEH ($p=0.008$). Among the secondary outcomes, no regression was associated with infrequent menstrual bleeding ($p=0.04$), and a diagnosis of EEC instead of AEH ($p<0.001$), while relapse was associated with longer menstrual cycles ($p=0.007$). At multivariate analyses, odds ratio for treatment failure was 4.54 (95% confidence interval [CI], 0.24–84.4) for a diagnosis of EEC instead of AEH ($p=0.3$), and 2.10 (95% CI, 1.03–4.29) for longer menstrual cycles ($p=0.042$), while infrequent menstrual bleeding perfectly predicted treatment failure.

Conclusions: Longer menstrual cycles and infrequent menstrual bleeding appear as independent predictive factors for conservative treatment failure in AEH and EEC. Further and larger studies are necessary to confirm these findings.

Keywords: hysteroscopy, fertility-sparing, endometrioid adenocarcinoma, progestogen, progesterone, progestin

Introduction

Endometrial hyperplasia is characterized by proliferation of endometrial glands resulting in increased gland to stroma ratio compared with proliferative endometrium.[1] Endometrial hyperplasia may be either a benign proliferation or a precancerous lesion; the latter one is termed ''atypical endometrial hyperplasia'' (AEH) by the 2014 World Health Organization classification, and is characterized by closely crowded glands with little intervening stroma and cytologic atypia; several other morphologic and immunohistochemical parameters may aid in the diagnosis of AEH.[1–12] AEH is the precursor of endometrioid endometrial adenocarcinoma, considered the most common histological type and representing the most prevalent gynecologic cancer in the Western world.[13–15]

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Although total hysterectomy is considered the gold standard treatment for AEH and endometrial cancer, many patients need a conservative treatment to preserve fertility or to avoid any surgical risk. Conservative treatment includes progestins with or without hysteroscopic resection, and follow-up biopsies every 3–6 months.[3,16–19] Such an approach may also be adopted for early endometrial cancer (EEC) in the case of endometrioid type, tumor grade 1, absence of extrauterine metastases, and absence of lymphovascular space, myometrial, or cervical invasion.[18] Several oral or intrauterine progestogens have been used, including medroxyprogesterone acetate, megestrol acetate, norethindrone acetate, and levonorgestrel-releasing intrauterine device (LNG-IUD).[3,18,20] However, a variable percentage of conservatively treated women shows unfavorable outcomes, with no regression of the disease, progression to cancer, relapse after a regression, or failure to achieve pregnancy after treatment.[21] Therefore, great efforts have been made in the search for predictive markers of response to conservative treatment.

Several clinical predictive factors along with histological, molecular, and imaging modalities have been studied to better understand the response to conservative management of AEH and EEC.[22–31] Among the clinical predictive factors of response to conservative treatment, age at diagnosis, previous pregnancies, obesity, history of infertility, histology type, the diagnosis of polycystic ovary syndrome (PCOS), hormonal therapy, menstrual cycle characteristics, and diabetes mellitus have been proposed, but their usefulness in predicting the response to treatment is still unclear.[22,23,27,32–37]

Identifying risk factors of treatment failure of patients with AEH and EEC is of paramount importance in counseling the patient who desire conservative management of these conditions. The aim of this study was to determine the role of several clinical factors in the prediction of treatment failure in patients diagnosed with AEH or EEC undergoing conservative management with hysteroscopic resection of the lesion and LNG-IUD insertion.

Materials and Methods

The present study is a single-center retrospective observational study following a protocol defined *a priori*, reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[38]

The medical records and pathology reports of all consecutive patients up to 45 years of age diagnosed with AEH or ECC who underwent conservative treatment with hysteroscopic resection followed by LNG-IUD insertion at the Department of Neuroscience, Reproductive Sciences, and Dentistry or at the Department of Public Health of University Federico II (Naples, Italy), from January 2007 to June 2018 were reviewed for assessing the associations of several clinical factors with the response to treatment. Additional data were obtained by administrating a telephone questionnaire to each included patient.

Exclusion criteria were the following:

- patients treated with hysterectomy;
- follow-up period <1 year;
- absence of written informed consent for the use of own biospecimens for research purposes;
- missing data after review of the medical records and unable to obtain the information after completion of the telephone questionnaire.

The preoperative management, treatment, and follow-up protocol of these conditions at our institution had been previously reported.[18]

All the pathology slides were reviewed by two blinded authors (L.I. and A.T.) to confirm the initial diagnosis. Disagreements were resolved by discussion at a two-headed microscope.

The primary outcome was the association of each clinical factor with treatment failure. Secondary outcomes were the associations of each clinical factor with: (1) no regression of disease, (2) relapse of the disease, or (3) achievement of successful pregnancy after treatment. Treatment failure was defined as a combined adverse outcome of treatment, including (1) no regression of disease and (2) relapse of the disease. Regression of the disease was defined as absence of any pretreatment lesions (AEH or EEC) in two consecutive histological examination performed at the 3- and 6-month follow-up hysteroscopy with endometrial biopsies under direct visualization. Relapse of the disease was defined as the presence of AEH or EEC after a previous regression.

The clinical factors considered in the analysis of association with the outcomes of response to treatment were: body mass index (BMI), cigarette smoking habit, hypertension, mean age at menarche, mean menstrual cycle length, mean menses length, heavy menstrual bleeding with or without prolonged menstrual bleeding, infrequent menstrual bleeding, frequent menstrual bleeding, irregular nonmenstrual vaginal bleeding, vaginal discharge at the time of biopsy, history of previous pregnancies, PCOS, sterility or infertility, family history of endometrial cancer, family history of leukemia, family history of thyroid disease, previous personal history of nonendometrial cancer diagnosis, use of oral contraceptives, hormone administration for assisted reproductive technology (ART), pelvic pain before endometrial biopsy, pathology diagnosis (AEH or EEC), and mean length of therapy. A detailed description of the clinical factors as defined at the time of diagnosis is reported in Supplementary Data S1.

The potential associations between each clinical factor and each outcome of response to conservative treatment (treatment failure, no regression, relapse, successful pregnancy after treatment) were initially assessed with standard univariate analyses: chi-squared test for categorical variables, *t*-test and Kruskal–Wallis test for normally distributed and non-normally distributed continuous variables, respectively (distribution was assessed with Shapiro–Wilk test).

The potential independent predictors of response to treatment were then evaluated using multivariate logistic regression. Covariates were selected for inclusion in the final model using a stepwise forward process with the following criteria: (1) p-value <0.05 at univariate analysis, and (2) clinical relevance. To reduce the potential overfitting due to the small number of successes (defined as treatment failure), a minimum events-to-variable ratio of 10 was maintained in all phases of model building; Schoenfeld's test was carried out to check the validity of proportional hazards assumption. A standard power analysis for sample size calculation was not performed, as most clinical factors considered had not yet been assessed in the literature.

As a separate additional analysis, the relationship between pathology diagnosis (AEH or EEC) and each clinical factor and treatment outcome (treatment failure, no regression, relapse, successful pregnancy after treatment) was evaluated comparing the distribution of all outcomes and clinical factors in women with AEH and in those with EEC.

A p-value of <0.05 was considered significant for all analyses, which were carried out using Stata, version 13.1 (Stata Corp., College Station, TX; 2013).

The present study received approval by the Institutional Review Board ''Carlo Romano'' of the University of Naples Federico II. All included patients signed an informed written consent for the use of their biospecimens for research purposes, and all data were anonymized to prevent the identification of the subjects.

Results

Patient characteristics

A total of 43 patients meeting the inclusion criteria were included in this study: 37 (86%) were diagnosed with AEH and 6 (14%) with EEC. The mean age was 36.0 ± 5.7 years. The mean BMI was 28.5 ± 7.6 kg/m^2. Personal history of hypertension was reported by 14% of the patients, 39.5% had previous pregnancies, 16.7% had the personal history of PCOS diagnosis, and 7.1% reported personal history of sterility or infertility. Family history of endometrial cancer was present in 9.3% of the patients, 23.3% reported family history of leukemia, and 27.9% of thyroid disease. Personal history of previous nonendometrial cancer diagnosis was found in 15.4% of the patients, 16.7% reported pelvic pain, and 4.8% reported vaginal discharge at the time of the endometrial biopsy resulting in the diagnosis of AEH or EEC. The mean age at menarche was 11.6 ± 1.2 years, menstrual cycle length 28.8 ± 3.5 days, and menses length 4.6 ± 1.3 days. A total of 33.3% of women reported heavy menstrual bleeding with or without prolonged menstrual bleeding, 4.8% reported infrequent menstrual bleeding, 7.1% reported frequent menstrual bleeding, 9.5% reported frequent irregular nonmenstrual vaginal bleeding. Regarding the use of oral contraceptives, 29.3% of patients never used oral contraceptives and 26.2% never received hormone administration for ART. The 16.7% of the patients identified themselves as smokers. The mean length of therapy was 26.6 ± 23.1 months, given that some patients who achieved complete regression of the disease elected to leave the LNG-IUD *in situ* as contraceptive device and some patients who experimented relapse refused hysterectomy and chose a second cycle of conservative treatment after re-evaluating risks and providing a new written informed consent.

Regarding treatment outcomes, 32.7% of women showed treatment failure (9.3% had no regression, and 23.3% experimented relapse). A second regression after relapse was observed in 44.4% of women who underwent a second cycle of conservative treatment. A successful pregnancy after treatment was achieved in 23.3% of the patients who attempted to conceive.

Outcomes and clinical factors are presented by pathology diagnosis (AEH and EEC) in Table 1.

Clinical predictive factors of response to treatment

Among all 23 clinical factors assessed as predictive of response to conservative treatment in women with AEH and EEC, 3 factors showed a significant association with at least one treatment outcome at univariate analyses. In particular, treatment failure was significantly associated with a longer menstrual cycle ($p = 0.002$), infrequent menstrual bleeding (two or less episodes in a 90 days period) ($p = 0.04$), and a diagnosis of EEC instead of AEH ($p = 0.008$). Among the secondary outcomes, infrequent menstrual bleeding ($p = 0.04$), and a diagnosis of EEC instead of AEH ($p < 0.001$) were significantly associated with no regression of the disease, while relapse of the disease was significantly associated with a longer menstrual cycle ($p = 0.007$). No clinical factor was significantly associated with successful pregnancy after treatment.

All univariate analyses assessing association between the clinical factor and each outcome are reported in Table 2.

At the multivariate logistic regression analysis, a longer menstrual cycle was significantly associated with treatment failure (odds ratio [OR] = 2.10; 95% confidence interval [CI], 1.03–4.29; $p = 0.042$), while a diagnosis of EEC instead of AEH was not associated to treatment failure (OR = 4.54; 95% CI, 0.24–84.4; $p = 0.3$). Since infrequent menstrual bleeding perfectly predicted the outcome, the variable was dropped by the model (Table 3).

Discussion

Main findings and interpretation

Our study assessed the role of 23 clinical factors in the prediction of the response to treatment in women with AEH and EEC undergoing conservative management. Three clinical risk factors, (1) longer menstrual cycle, (2) diagnosis of EEC instead of AEH, and (3) infrequent menstrual bleeding, were significantly associated with a treatment failure. Moreover, a longer menstrual cycle was also significantly associated with relapse of the disease, whereas a diagnosis of EEC instead of AEH and infrequent menstrual bleeding were also significantly associated with no regression. However, at the multivariate analyses, only a longer menstrual cycle and infrequent menstrual bleeding significantly predicted treatment failure.

Our results are in agreement with prior published studies in which longer menstrual cycles and infrequent menstrual bleeding are linked to chronic anovulation or ovarian dysfunction, which have been associated with lower rates of response of AEH and/or EEC to conservative treatment.[36,39] The reason may be found in the pathogenesis of AEH and EEC, as a consequence of a continuous estrogenic action over the endometrium unopposed by progesterone.[40,41] Such imbalance is the basis of the use of progestins as conservative treatment for these lesions. Other conditions such as infrequent menstrual bleeding or long menstrual cycles might cause an excess of endogenous estrogens that antagonizes the progestin therapeutic action. Our finding, if confirmed on other larger cohorts, will help counseling patients, promoting a closer follow-up and/or a different treatment protocol (e.g., association of progestins, higher progestin dose, higher treatment length) for patients with long menstrual cycles and/or infrequent menstrual bleeding.

Regarding other clinical factors, which did not show predictive value in our study, results of previous studies are conflicting. In particular, we found no predictive value for having personal history of PCOS, sterility/infertility,

Table 1. Pretreatment Clinical Factors and Primary and Secondary Outcomes, Overall, and by Histological Diagnosis

Variables	*All women* (n = *43*)	*AEH diagnosis* (n = *37*)	*EEC diagnosis* (n = *6*)
Pretreatment clinical factors			
Mean age at the time of diagnosis, SD	36.0 (5.7)	36.1 (5.9)	35.5 (4.5)
Mean BMI in kg/m^2, SD	28.5 (7.6)	27.9 (7.6)	32.4 (7.1)
Cigarette smoke, %	16.7	16.7	16.7
Hypertension, %	14.0	13.5	16.7
Mean age at menarche in years, SD	11.6 (1.2)	11.6 (1.2)	11.3 (1.4)
Mean menstrual cycle length in days, SD	28.8 (3.5)	28.2 (2.6)	32.3 (5.1)
Mean menstrual phase length in days, SD	4.6 (1.3)	4.4 (1.3)	5.4 (1.1)
Heavy menstrual bleeding with or without prolonged menstrual bleeding, %	33.3	30.6	50.0
Infrequent menstrual bleeding, %	4.8	2.8	16.7
Frequent menstrual bleeding, %	7.1	5.6	16.7
Irregular nonmenstrual bleeding, %	9.5	11.1	0.0
Vaginal discharge, %	4.8	5.6	0.0
Previous pregnancies, %	39.5	43.2	16.7
PCOS diagnosis, %	16.7	16.7	16.7
Sterility or infertility, %	7.1	5.6	16.7
Family history of endometrial cancer, %	9.3	10.8	0.0
Family history of leukemia, %	23.3	18.9	50.0
Family history of thyroid diseases, %	27.9	29.7	16.7
Previous nonendometrial cancer diagnosis, %	15.4	17.4	0.0
Use of oral contraceptives, %	29.3	31.4	16.7
Use of hormone administration for assisted reproductive technology, %	26.2	27.8	16.7
Pelvic pain, %	16.7	19.4	0.0
Mean length of therapy in months, SD	26.6 (23.1)	26.5 (23.4)	27.5 (23.5)
Post-treatment outcomes[a]			
Regression, %	90.7	100	33.3
AEH/EEC relapse, %[b]	23.3	21.6	50.0
Treatment failure (No regression/relapse), %*	32.6	21.6	83.3
Postrelapse regression, %[c]	44.4	50.0	0.0
Successful pregnancies after treatment, %	23.3	27.0	0.0

Given the very few women with a diagnosis of EEC, the analyses were severely underpowered to detect any significant difference in the distribution of the recorded exposures between the two groups. The only comparison achieving statistical significance ($p < 0.05$) was identified with the "*" ($p = 0.02$). All other p that were not reported were >0.05.

[a]The raw number of women experiencing at least one outcome among those reported is: regression: $n = 39$; relapse: $n = 10$; postrelapse regression: $n = 4$; successful pregnancy after treatment: $n = 10$.

[b]Four missing values.

[c]$n = 10$ women with relapse.

BMI, body mass index; SD, standard deviation; PCOS, polycystic ovary syndrome; AEH, atypical endometrial hyperplasia; EEC, early endometrial cancer.

previous pregnancies, or obesity, which is in agreement with studies by other authors.[23,36,42] However, other studies reported personal history of PCOS to be both a risk factor for endometrial cancer (three times increased risk)[43] and a predictive factor of poor response to conservative treatment in AEH and EEC.[33] In fact, PCOS has been associated with metabolic features that increase the risk of cancer (e.g., hyperinsulinism, insulin resistance, hyperandrogenism, and hyperglycemia), it is unclear if the increased risk of endometrial cancer may be due to PCOS itself or to other related risk factors.[33] An explanation of a PCOS-specific risk might be that both serum estrogens and androgen levels are significantly elevated in patients with PCOS. Thus, endogenous estrogen levels may be increased also by peripheral conversion of androgens to estrogens.[33] In addition, other findings seem also to indicate a progestin resistance at the level of the endometrium of women with PCOS as a result of an inflammatory microenvironment induced by insulin resistance associated with PCOS.[33,34,37,44–47] However, given the conflicting findings, the predictive value of PCOS is still uncertain.

Regarding infertility and previous pregnancies, a systematic review and meta-analysis found that they were associated with regression of AEH and EEC.[23] Such results are in contrast with our findings. However, those authors did not find a clear pathophysiological explanation for such associations, concluding that there is need of confirmation by larger studies.

Regarding obesity, we found no predictive of treatment failure value, in contrast with results of other studies that reported poor response to conservative treatment in obese patients.[36,37,39,48,49] The possible effect of obesity on the response to progestins might lie in an excess of endogenous estrogens, as a consequence of chronic hyperinsulinemia and

Table 2. Pretreatment Clinical Factors and Univariate Analyses Evaluating Their Relationship with Each Outcome

Pretreatment clinical factors	*Overall* (n=*43*)	*Treatment failure* (n=*14*)	p*	*Regression* (n=*39*)	p*	*No regression* (n=*4*)	p*	*Relapse* (n=*10*)	p*	*Pregnancy after treatment* (n=*10*)	p*
Mean BMI in kg/m^2, SD	28.5 (7.6)	30.6 (8.4)		30.4 (9.2)		28.3 (7.5)		30.7 (8.7)		30.0 (9.6)	
Cigarette smoke, %	16.7	7.2						0.0		20.0	
Hypertension, %	14.0	7.1		25.0		12.8		0.0		10.0	
Mean age at menarche in years, SD	11.6 (1.2)	11.8 (1.6)		11.8 (0.9)		11.6 (1.2)		11.8 (1.7)		11.9 (1.2)	
Mean menstrual cycle length in days, SD	28.8 (3.5)	31.0 (3.9)	0.002	28.5 (3.3)		31.5 (4.0)		30.8 (4.0)	0.007	28.1 (0.8)	
Mean menstrual phase length in days, SD	4.6 (1.3)	4.6 (1.3)		4.5 (1.3)		4.0 (1.3)		4.4 (1.3)		4.3 (1.0)	
Heavy menstrual bleeding with or without prolonged menstrual bleeding, %	33.3	35.7		34.2		25.0		40.0		20.0	
Infrequent menstrual bleeding, %	4.8	14.3	0.04	2.6	0.04	25.0	0.04	10.0		10.0	
Frequent menstrual bleeding, %	7.1	0.0		7.9		0.0		0.0		0.0	
Irregular nonmenstrual bleeding, %	9.5	0.0		10.5		0.0		0.0		10.0	
Vaginal discharge, %	4.8	7.1		5.3		0.0		10.0		10.0	
Previous pregnancies, %	39.5	35.7		41.0		25.0		40.0		40.0	
PCOS diagnosis, %	16.7	14.3		15.8		25.0		10.0		20.0	
Sterility or infertility, %	7.1	14.3		5.3		25.0		10.0		10.0	
Family history of endometrial cancer, %	9.3	7.1		10.3		0.0		10.0		0.0	
Family history of leukemia, %	23.3	21.4		20.5		50.0		10.0		20.0	
Family history of thyroid diseases, %	27.9	35.7		28.2		25.0		40.0		40.0	
Previous nonendometrial cancer diagnosis, %	15.4	0.0		16.7		0.0		0.0		25.0	
Use of oral contraceptives, %	29.3	38.5		32.4		0.0		55.6		10.0	
Hormone administration for assisted reproductive technology, %	26.2	28.6		26.3		25.0		30.0		10.0	
Pelvic pain, %	16.7	14.3		18.4		0.0		20.0		30.0	
Histological diagnosis, %											
AEH	86.0	64.3	0.008	94.9	<0.001	0.0	<0.001	90.0		100	
EEC	14.0	35.7		5.1		100		10.0		0.0	
Mean length of therapy in months, SD	26.6 (23.1)	29.8 (26.4)		26.6 (23.1)		26.5 (23.4)		36.5 (28.4)		28.1 (30.5)	

*Chi-squared test for categorical variables; *t*-test and Kruskal–Wallis test for normally distributed and non-normally distributed continuous variables, respectively. All other *p*-values that were not reported were >0.05. All *p*-values are referred to the comparison between the women versus those without the selected outcome: for example, women experiencing regression versus those without regression.

Table 3. Multivariate Analyses Evaluating the Potential Clinical Factors As Predictors of Therapeutic Failure

Variables	*OR (95% CI)*	p
Mean menstrual cycle length, 1-day increase	2.10 (1.03–4.29)	0.042
Histological diagnosis:		
AEH (ref. cat.)	1	—
EEC	4.54 (0.24–84.4)	0.3
Infrequent menstrual bleeding, yes vs no	(Omitted)[a]	—

[a]As infrequent menstrual bleeding perfectly predicted the outcome, the variable was dropped by the model.

OR, odds ratio; CI, confidence interval; ref. cat., reference category.

increased peripheral conversion of androgen to estrogens in adipose tissue; this may antagonize the action of progestins.[36,50] However, these authors did not perform a multivariate analysis that demonstrated the independent predictive value of obesity. Indeed, a recent systematic review and meta-analysis that assessed its predictive value at multivariate analysis showed no significant association,[23] which is concordant with our results.

With regard to the type of pathology diagnosis, we found significantly more frequent treatment failure and no regression for a diagnosis of EEC instead of AEH, as reported by previously published studies.[18,36,50] However, this predictive value was not independent, as shown at multivariate analysis.

Hormone administration for ART showed no predictive value of treatment failure in our analysis, in contrast with the results of another study in the literature, which showed that patients undergoing ART were more likely to achieve pregnancy ($p = 0.04$) at multivariate analysis[33]; however, no impact on the risk of treatment failure was found in that study, which is in concordance with our results. The use of fertility drugs (e.g., clomiphene citrate and gonadotropins) is associated with increased estrogen production during the follicular phase of the ovulation induction cycle.[51] Thus, a possible association between fertility drugs and the risk of endometrial cancer has been studied, with conflicting results.[52–57]

It is interesting to note that several immunohistochemical markers showed an association with the response of AEH and EEC to conservative treatment.[30] Among these, estrogen and progesterone receptors, Dusp6, GRP78, and mismatch repair proteins showed a predictive ability on pretreatment biopsies.[30] On the other hand, the expression of Bcl-2, ki67, and surviving showed an association with the response on post-treatment biopsies.[30] It would be interesting to combine clinical and immunohistochemical data to improve the tailoring of treatment and follow-up of patients with AEH and EEC.

Strengths and limitations

Our study has several aspects that are worth highlighting. To the best of our knowledge, our study evaluates the largest number of clinical factor ($n = 23$) in the prediction of response to conservative management of AEH and EEC in the literature. In addition, many risk factors are evaluated for the first time in this field. Moreover, our study is among the largest cohorts assessing clinical predictive factors of women with AEH.[58] Additionally, this is the first study assessing clinical predictive factors in women undergoing combined conservative treatment with hysteroscopic resection followed by LNG-IUD insertion. Such approach has recently been suggested to be more effective and safer than other conservative treatment options (e.g., oral progestins, LNG-IUD alone, hysteroscopic resection alone).[18] Lastly, another strength of our study is the thorough pathology review by two independent pathologists. This fact is crucial, given the inter and intraobserver variability in the assessment of endometrial specimens.[56,57,59–61]

We acknowledge several limitations of our study. The retrospective study design and the overall small size of the study population could limit the interpretation of the data. In fact, the perfect prediction found for infrequent menstrual bleeding might be due to the high number of covariates compared with the sample size. However, a greater sample size and a prospective study design are difficult to obtain in a single center, as only 20%–25% of endometrial cancer and AEH occur in premenopausal women, and only 3%–5% of women diagnosed with endometrial cancer are younger than 45 years of age.[62]

Conclusion

Among the 23 clinical factors assessed in the prediction of the response to conservative management of AEH and EEC, a longer menstrual cycle and infrequent menstrual bleeding are independent predictive clinical factors for treatment failure. Patients with those clinical features may have an increased risk of treatment failure and might benefit from a closer follow-up, and a different treatment protocol. Further and larger studies are necessary to confirm our findings.

Ethics Approval

The present study received approval by the Institutional Review Board ''Carlo Romano'' of the University of Naples Federico II.

Consent to Participate

All included patients signed an informed written consent.

Consent for Publication

All included patients signed an informed written consent.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

A.R.: study conception, study design, study methods, data analysis, article preparation, methods supervision, whole study supervision; A.T.: study conception, study design, study methods, data analysis, article preparation, methods supervision; M.E.F.: study design, study methods, data analysis, article preparation; M.I: study design, study methods, data collection, article preparation; A.M.: study conception, data collection, data analysis, responsible surgeon;

M.G.: study conception, data analysis, responsible surgeon, methods supervision; L.I.: study conception, data analysis, responsible pathologist, whole study supervision; A.D.S.: study conception, data analysis, responsible surgeon, article preparation, whole study supervision; J.C.: study design, data analysis, article preparation, methods supervision, whole study supervision; F.Z.: study conception, study design, data analysis, responsible surgeon, methods supervision, whole study supervision.

Author Disclosure Statement

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Supplementary Material

Supplementary Data

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