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Mismatch repair-deficiency specifically predicts recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment: A multi-center study

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HIGHLIGHTS

- AEH and EEC with MMR deficiency previously appeared to be resistant to progestins
- MMR-deficiency does not predict resistance of AEH/EEC to hysteroscopic resection plus progestin
- MMR-deficiency predicts AEH/EEC recurrence with 100% specificity
- In young patients with AEH/EEC, hysteroscopic resection plus progestin might provide a window period to attempt pregnancy
- MMR-deficient patients with AEH/EEC should be closely and carefully followed due to the high risk of recurrence

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ABSTRACT

Objective. Deficient expression of mismatch repair proteins (MMR) has been suggested to be a predictor of resistance of atypical endometrial hyperplasia (AEH) and early endometrial carcinoma (EEC) to conservative treatment.

Aims. To assess the predictive value of MMR immunohistochemistry in patients conservatively treated for AEH and EEC, and to calculate its predictive accuracy.

Materials and methods. All patients with AEH or EEC conservatively treated with hysteroscopic resection plus progestins in two referral centers from January 2004 to July 2019 were retrospectively assessed. Immunohistochemistry for MMR was *ad hoc* performed. Study outcomes were: (i) the association of a deficient immunohistochemical expression of MMR with resistance and recurrence of AEH and EEC after conservative treatment, and (ii) the accuracy of MMR immunohistochemistry in predicting the outcome of conservative treatment. Relative risk (RR) for the associations, and sensitivity, specificity and area under the curve (AUC) on receiver operating characteristic curve for the predictive accuracy were calculated.

Results. Sixty-nine women, (47 AEH and 22 EEC) were included; deficient MMR expression was observed in 8.7% of cases. Resistance to conservative treatment was more common in MMR-deficient than MMR-proficient cases (33.3% *vs* 15.9%; RR = 2.1), but with no statistical significance ($p = 0.2508$). On the other hand, recurrence was significantly more common in MMR-deficient than MMR-proficient cases (100% *vs* 26.4%; RR = 3.8; $p < 0.0001$). In predicting recurrence, a deficient immunohistochemical expression of MMR showed sensitivity = 22.2%, specificity = 100%, and AUC = 0.61.

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Conclusion. Deficient MMR immunohistochemical expression does not imply resistance of AEH/EEC to conservative treatment. On the other hand, MMR-deficiency appears as a highly specific predictor of recurrence of AEH/EEC after initial regression.

1. Introduction

Endometrial hyperplasia is an irregular proliferation of endometrial glands resulting in an increased gland to stroma ratio when compared to proliferative endometrium [1]. It may be either a benign condition (*i.e.* benign endometrial hyperplasia) or a precancerous lesion (*i.e.* atypical endometrial hyperplasia, AEH); these two conditions may be differentiated based on histomorphological features and/or the expression of several immunohistochemical markers [1–6]. AEH is the precursor of endometrioid endometrial adenocarcinoma, the most common histotype of the most prevalent cancer in women of Western countries [7–9].

Although total hysterectomy with bilateral salpingo-oophorectomy is the gold standard treatment for AEH and endometrial cancer, a conservative treatment is necessary in patients desiring pregnancy or in patients at high surgical risk [10]. Conservative treatment consists of oral or intra-uterine progestins with or without hysteroscopic endometrial resection, and follow-up biopsies every 3–6 months [10–14]. In the case of early endometrial carcinoma (EEC), eligibility criteria for conservative treatment are: endometrioid histotype, International Federation of Gynecology and Obstetrics (FIGO) tumor grade 1, absence of extrauterine metastases, and absence of lymphovascular space invasion, myometrial or cervical invasion [13]. Unfortunately, a variable percentage of patients shows unfavourable outcomes of conservative treatment, such as no regression of the disease, recurrence, progression to more advanced disease, or failure to achieve pregnancy [15]. For this reason, the search for predictive markers of response to conservative treatment appears crucial.

In the last years, several clinical, histological and immunohistochemical markers have been assessed for this purpose [16–26]. However, no marker has shown a predictive accuracy so high that it can be used as a stand-alone marker. Among the assessed immunohistochemical markers, mismatch repair proteins (MMR) appeared as one of the most promising markers; in fact, Zakhour et al. [27] and Chung et al. [28] showed that MMR-deficient AEH and EEC failed to achieve a complete regression in almost all cases. However, such studies did not perform hysteroscopic resection before progestin therapy, which appears to be associated with better outcomes [29,30]. Furthermore, the accuracy of MMR as predictive marker was never calculated.

On this account, the aims of this study were: 1) to determine the predictive role of MMR-deficiency in AEH and EEC conservatively treated with hysteroscopic resection plus progestins; 2) to calculate the accuracy of MMR as predictive marker in conservatively treated AEH and EEC.

2. Materials and methods

2.1. Study protocol and selection criteria

The study was performed following an *a priori* defined study protocol and was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and checklist [31]. The study was designed as a multi-center observational study evaluating a retrospective cohort.

Medical records and pathology reports of all consecutive patients up to 45 years of age who underwent conservative treatment with hysteroscopic resection plus progestin for AEH or EEC at the Department of Neuroscience, Reproductive Sciences and Dentistry and at the Department of Public Health of the University Federico II, Naples, Italy, and at the Department of Woman and Child Health, Agostino Gemelli University Polyclinic of the Catholic University of the Sacred Heart, Rome, Italy, from January 2004 to July 2019.

Ad hoc histological sections were obtained from paraffin blocks of pre-treatment endometrial biopsy in order to assess the association of MMR immunohistochemical expression and outcomes of conservative treatment, as well as the accuracy of MMR immunohistochemistry in the prediction of the response to treatment. Before immunohistochemical analysis, histological slides of all patients satisfying the selection criteria were reviewed in order to confirm the initial diagnosis of AEH and G1 EEC, based on the WHO criteria [1]. The presence of extrauterine metastases, lymphovascular space invasion, myometrial or cervical invasion had been excluded at the time of diagnosis based on ultrasound scan/magnetic resonance imaging and histological examination of the hysteroscopic resection specimen.

A priori exclusion criteria were: patients who underwent hysterectomy; follow-up length < 1 year; patients not providing a written informed consent for the use of own biospecimens for research purposes; patients with no available tissue for *ad hoc* immunohistochemistry.

Conservative treatments included hysteroscopic resection followed by levonorgestrel-releasing intrauterine system (LNG-IUD) insertion ($n = 36$) or megestrol acetate (MA) administration ($n = 33$). Patients pre-operative management, hysteroscopic resection, LNG-IUD insertion and follow-up type were performed according to previously described methods [12].

2.2. Study outcomes

The study outcome were:

- the association of a deficient immunohistochemical expression of MMR with resistance AEH or EEC to conservatively treated patients;
- the association of a deficient immunohistochemical expression of MMR with recurrence of AEH or EEC in conservatively treated patients;
- the accuracy of immunohistochemistry for MMR in predicting each outcome of conservative treatment that showed significant association with MMR expression.

Regression of AEH or EEC was defined as the absence of any pretreatment lesions at histological examination of two consecutive follow-up hysteroscopic biopsies; resistance was defined as no regression within 12 months after the beginning of the treatment. Recurrence of the disease was defined as a new diagnosis of AEH or EEC after a previous complete regression.

The immunohistochemical expression of MMR was assessed by considering the expression of MLH1, MSH2, MSH6 and PMS2 ($n = 33$), or only MSH and PMS2 ($n = 36$), since a combination of only two MMR may be used as a still cheaper test without affecting the diagnostic accuracy in detecting microsatellite instability [32]. MMR expression was dichotomized as “proficient” and “deficient”; the criteria proposed by the British Association of Gynaecological Pathologists were adopted [33].

2.3. Histological and immunohistochemical methods

Histological and immunohistochemical methods followed previously described methods [34]. We adopted anti-MLH1 Mouse Monoclonal Primary Antibody (prediluted, Ventana, Clone M1), anti-MSH2 Mouse Monoclonal Antibody (prediluted, Ventana, Clone G219–1129) anti-MSH6 Rabbit Monoclonal Primary Antibody (prediluted, Ventana,

Clone SP93) and anti-PMS2 Mouse Monoclonal Primary Antibody (prediluted, Ventana, Clone A16–4).

Histological slides were assessed by two expert gynecologic pathologists for each centre (LI and AT for the University of Naples Federico II, and SS and GFZ for the Catholic University of the Sacred Heart), who were blinded to the treatment outcomes; disagreements were solved by discussion at a two-headed microscope.

2.4. Statistical analysis

The association of a MMR-deficient expression with each conservative treatment outcome was assessed by using the relative risk (RR) with 95% confidence intervals (CI) and a significant p-value <0.05.

The accuracy of MMR immunohistochemistry in predicting the outcome of treatment was assessed for the outcomes that showed a significant association with MMR status. Predictive accuracy was calculated as sensitivity, specificity and area under the curve (AUC) on receiver operating characteristic (ROC) curves. AUC thresholds to judge MMR predictive accuracy was *a priori* defined. In particular, accuracy was considered as null for AUC ≤ 0.5, low for 0.5 < AUC ≤ 0.75, moderate for 0.75 < AUC ≤ 0.9, high for 0.9 < AUC < 0.97, very high for AUC ≥ 0.97, as previously reported [5,6].

A subgroup analysis of MMR predictive accuracy was performed based on the administration route of progestins: local (*i.e.* LNG-IUD) or systemic (*i.e.* MA).

Statistical analyses were performed using SPSS 19.0 package (SPSS Inc., Chicago, IL, USA).

2.5. Ethical statement

The study received approval by the Institutional Review Board of the University of Naples Federico II and the Catholic University of the Sacred Heart. All included patients signed an informed written consent for the use of their biospecimens for research purposes, and all data were anonymized in order to avoid the identification of the subjects. The whole study was performed in accordance with the Declaration of Helsinki.

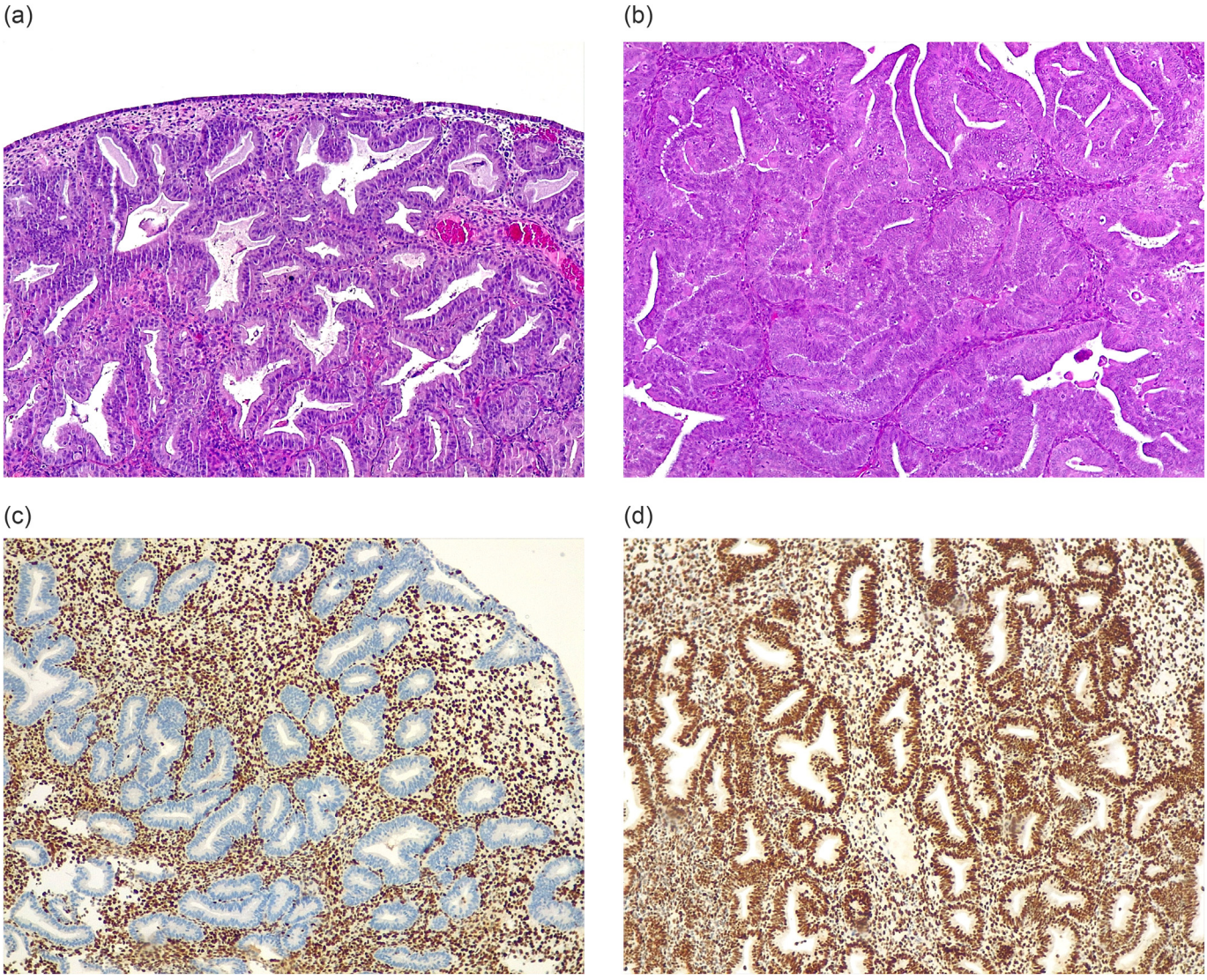

Fig. 1. Morphological and immunohistochemical features of index biopsies (magnification 100×). a) Complex, crowded glands in a case of atypical endometrial hyperplasia. b) Confluent, maze-like glands in a case of early endometrial carcinoma. C) Loss of MSH6 expression; note the negative staining (blue) in the glands of the lesion compared to the positive staining (brown) in the background stromal cells. d) Intact PMS2 expression; positive staining (brown) in both the glands of the lesion and the background stroma. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patients' characteristics.

Patients characteristics	N (%)	MEAN ± SD
Age, years	–	35.5 ± 5.7
Body Mass Index, kg/m^2	–	29.1 ± 8.5
Diagnosis of early endometrial carcinoma	22 (31.9)	–
Diagnosis of atypical endometrial hyperplasia	47 (68.1)	–
Previous pregnancies	23 (33.3)	–
Spontaneous delivery	4 (5.8)	
Cesarean section	8 (11.6)	
Miscarriages	15 (21.7)	
Familiar history of endometrial carcinoma	2 (2.9)	–
Familiar history of other cancers	20 (29)	–
Other diseases		–
Blood hypertension	5 (7.2)	
Diabetes mellitus	4 (5.8)	
Thyroid diseases	11 (15.9)	
Endometriosis	3 (4.3)	
Infertility	2 (2.9)	
Polycystic ovarian syndrome	7 (10.1)	
Symptoms		–
Heavy menstrual bleeding with or without prolonged	16 (23.1)	
menstrual bleeding	11 (15.9)	
Frequent irregular non-menstrual vaginal bleeding	2 (2.9)	
Frequent menstrual bleeding	9 (13)	
Pelvic pain		
Administration route of progestins		
Local (levonorgestrel-releasing intrauterine system)	36 (52.2)	
Systemic (Megestrol acetate)	33 (48.8)	
Treatment outcomes		–
Regression	57 (82.6)	
Resistance	12 (17.4)	
Recurrence	18 (31.6)	
Follow-up length, months	–	54.8 + 34.4

3. Results

3.1. Patients' characteristics

A total of 69 women were included in the study: 47 (68.1%) with AEH and 22 (31.9%) with EEC (Fig. 1).

The mean age ± standard deviation (SD) at diagnosis was 35.5 ± 5.7 years (range 20–46), while the mean BMI ± SD was 29.1 ± 8.5 Kg/m^2 (range 18.3–56.6); 33.3% of women had previous pregnancies, 2.9% a familiar history of endometrial carcinoma, and 29% a familiar history of other cancers. Among other diseases, 15.9% of women reported thyroid diseases, 10.1% polycystic ovarian syndrome, 7.2% blood hypertension, 5.8% diabetes mellitus, and 4.3% endometriosis. Among symptoms, 33.3% of women reported heavy menstrual bleeding with or without prolonged menstrual bleeding, 5.6% frequent irregular non-menstrual vaginal bleeding, 5.6% frequent menstrual bleeding, and 2.9% infertility (Table 1).

Regarding treatment, after hysteroscopic resection, 36 (52.2%) women underwent LNG-IUD insertion, and 33 (47.8%) underwent MA administration. Overall, 17.4% of women showed resistance to treatment, while 31.6% of women who responded showed a subsequent recurrence. The mean ± SD of follow-up time was 54.8 + 34.4 months (Table 1).

3.2. Main analysis

On immunohistochemistry, 6 patients (8.7%) showed a deficient immunohistochemical expression of MMR (Fig. 1). Three of the MMR-deficient cases were AEH and 3 were EEC (Table 2). MMR-deficient cases showed resistance to treatment more commonly than MMR-proficient cases (33.3% *vs* 15.9%), with a RR of 2.1 (95%CI: 0.6–7.5) but with no statistical significance ($p = 0.2508$). Recurrence of AEH/EEC after a complete regression occurred significantly more commonly in MMR-deficient cases than MMR-proficient cases (100% *vs* 26.4%), with a RR of 3.8 (95%CI: 2.4–5.9, $p < 0.0001$). In predicting recurrence of disease after a complete regression, a deficient immunohistochemical expression of MMR showed sensitivity = 22.2%, specificity = 100%, and AUC = 0.61 (95%CI: 0.44–0.76, Fig. 2).

3.3. Subgroup analysis

Among MMR-deficient cases, recurrence occurred after 24 and 39 months in the LNG-IUD group, and after 12 and 18 months in the MA group (Table 2). In predicting recurrence of disease after a complete regression, a deficient immunohistochemical expression of MMR showed sensitivity = 50%, specificity = 100%, and AUC = 0.75 (95%CI: 0.00–1.00) in the LNG-IUD subgroup (Fig. 3), and sensitivity = 14.3%, specificity = 100%, and AUC = 0.57 (95%CI: 0.35–0.79) in the MA subgroup (Fig. 4).

4. Discussion

4.1. Main findings and interpretation

This study showed that, in young women undergoing hysteroscopic resection plus progestin AEH and EEC, MMR-deficiency does not appear as a significant predictor of resistance to treatment, but rather as a predictor of recurrence with 100% specificity.

MMR includes four main proteins (MLH1, MSH2, MSH6, PMS2), whose deficiency is responsible for microsatellite instability (MSI) [32]. MSI is a condition associated with high mutational load, and is commonly found in several human malignancies, especially colorectal,

Table 2
Characteristics of MMR-deficient cases.

Case no.	AGE, years	BMI, kg/m^2	Familiarity for cancer	Index histological diagnosis	Deficient MMR protein	Progestin administered	Resistance (Diagnosis)	Recurrence (diagnosis)	Time to recurrence, months
1	33	19.5	Yes (colorectal carcinoma)	EEC	MSH6/MSH2	MA	No	Yes (AEH)	12
2	43	21.4	No	EEC	MSH6	LNG-IUD	Yes (EEC)	–	–
3	31	39.3	No	EEC	PMS2	LNG-IUD	Yes (AEH)	–	–
4	38	22.4	Yes (endometrial carcinoma)	AEH	MSH6	LNG-IUD	No	Yes (AEH)	24
5	37	24.6	No	AEH	MSH6	LNG-IUD	No	Yes (EEC)	39
6	34	22	No	AEH	PMS2	MA	No	Yes (AEH)	18

BMI: Body Mass Index.
EEC: early endometrial carcinoma.
AEH: atypical endometrial hyperplasia.
LNG-IUD: levonorgestrel-releasing intrauterine system.

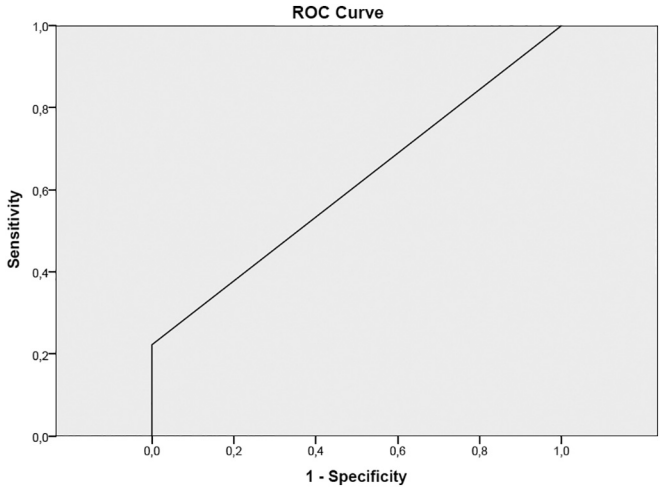

Fig. 2. Area under the curve (AUC) on receiver operating characteristic (ROC) curve of mismatch repair proteins deficiency in predicting recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment.

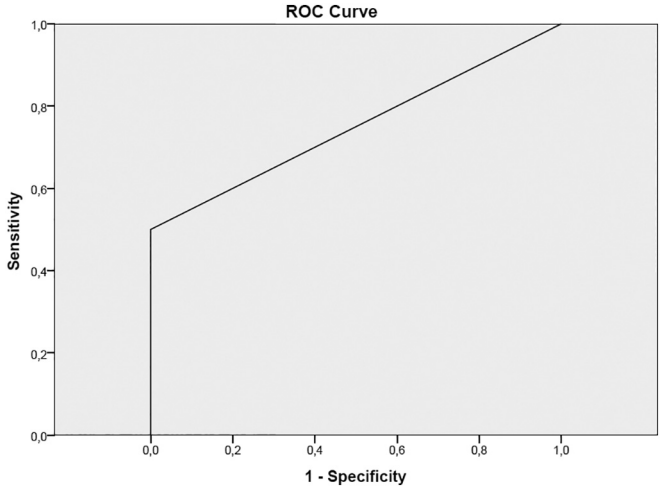

Fig. 3. Area under the curve (AUC) on receiver operating characteristic (ROC) curve of mismatch repair proteins deficiency in predicting recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment in the subgroup treated with LNG-IUD.

endometrial and gastric carcinoma [35–37]. In endometrial carcinoma, MSI defines one of the four prognostic groups identified by The Cancer Genome Atlas (TCGA) [32,38,39]. Among the TCGA groups of endometrial carcinoma, the MSI group shows intermediate prognosis and is mainly constituted by endometrioid carcinomas [38–40]. The MSI group shows high prevalence of unfavourable prognostic features such as high FIGO grade, lymphovascular space invasion and deep myometrial invasion; on the other hand, the high mutational load tends to produce a strong immune response which likely mitigates the tumor aggressiveness [39,41].

In order to make the TCGA classification widely applicable in the common practice, immunohistochemical surrogates of molecular prognostic markers have been used. In this regard, immunohistochemistry for MMR appeared as a reliable surrogate of MSI molecular testing [32,39].

The importance of MMR in conservatively treated AEH and EEC lies in the possibility that the MSI status may affect the responsiveness to progestins. In fact, previous studies showed that MMR-deficient AEH and EEC resisted to conservative treatment in more than 90% of cases [27,28]. However, those studies did not perform hysteroscopic resection, which might achieve a significant improvement in regression rates compared to progestins alone [29,30]. Furthermore, the accuracy of MMR as predictive marker has never been calculated.

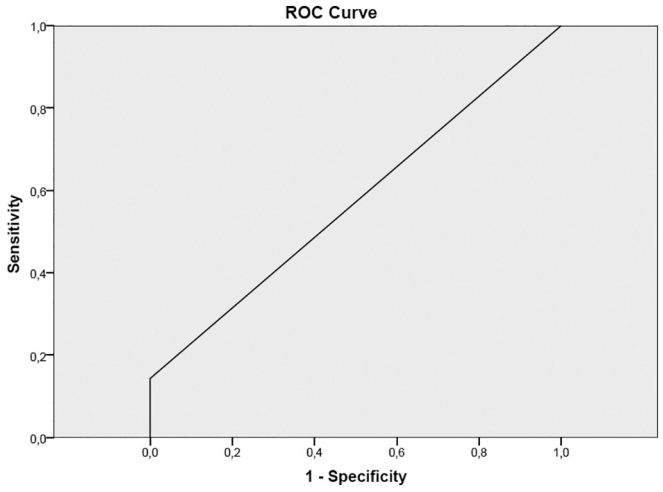

Fig. 4. Area under the curve (AUC) on receiver operating characteristic (ROC) curve of mismatch repair proteins deficiency in predicting recurrence of atypical endometrial hyperplasia and early endometrial carcinoma after conservative treatment in the subgroup treated with megestrol acetate.

In our study, we confirmed the overall unfavourable prognostic significance of MMR deficiency in conservatively treated AEH and EEC. In fact, we found that a deficient immunohistochemical expression of MMR was associated with a 2.1-fold increased risk of resistance and a 3.8-increased risk of recurrence compared to a retained MMR expression. We may reasonably hypothesize that the high mutational load consequent to MSI lead to the activation of alternative pathways that are less dependent on hormone receptors [27,42]. However, while previous studies showed resistance to conservative treatment in more than 90% of MMR-deficient AEH/EEC cases [27,28], we found that only one third of MMR-deficient cases resisted to treatment. The difference in the outcomes between our and previous studies might lie in the use of hysteroscopic resection before progestin therapy. Indeed, there is consistent evidence that hysteroscopic resection improves the effectiveness of conservative treatment of AEH/EEC [29,30]. In our series, it is possible that hysteroscopic resection allowed achieving an initial complete regression in most MMR-deficient cases. This finding suggests that hysteroscopic resection plus progestin might be proposed as the gold-standard conservative approach for MMR-deficient AEH and EEC. However, all MMR-deficient cases which regressed subsequently showed recurrence of disease, with a time to recurrence ranging from 12 to 39 months. The RR of recurrence was indeed higher than the RR of resistance (3.8 *vs* 2.1), and the latter one did not result statistically significant. Therefore, despite decreasing the likelihood of a complete regression, MMR deficiency seems to be a highly specific predictive marker of recurrence rather than of resistance. On the one hand, our findings support the possibility of achieving a complete regression in MMR-deficient AEH/EEC patients, through the use of hysteroscopic resection before progestins. On the other hand, the invariable risk of recurrence indicates the need for a closer and more careful follow-up in MMR-deficient AEH/EEC patients, given the possibility of progression to myoinvasive disease [43]. It might be appropriate to test whether more aggressive conservative treatments (*e.g.* hysteroscopic resection plus LNG-IUD plus systemic progestins, or higher dose of progestins) would achieve better results in MMR-deficient AEH and EEC.

It should be remarked that the overall predictive accuracy of MMR was low, as indicated by the AUC values. Therefore, it appears clear

that MMR could not work as a stand-alone predictive marker in conservatively treated AEH and EEC. In fact, while a deficient MMR expression would indicate a lower likelihood of response and a virtually certain risk of recurrence, a retained MMR expression would not be highly informative about the outcome of the treatment.

Lastly, we also performed a subgroup analysis based on the administration route of progestins. The first subgroup was treated with hysteroscopic resection plus LNG-IUD insertion, which may be the most effective conservative treatment for AEH and EEC [12,14,44], while the second subgroup was treated with hysteroscopic resection plus MA. The specificity for recurrence was 100% in both subgroups, although the sensitivity was lower in the MA subgroup. The lower sensitivity might be due to the lower effectiveness of MA compared to LNG-IUD. In fact, while the resistance rate was similar between the two groups (16.7% for LNG-IUD and 18.2% for MA), the recurrence rate was considerably lower in the first group (13.3% *vs* 51.6%). Therefore, patients treated with MA appear more likely to show recurrence even in the case of retained MMR expression. Interestingly, MMR-deficient patients treated with LNG-IUD recurred later than MMR-deficient patients treated with MA (24–39 months *vs* 12–18 months). Although the number of MMR-deficient patients in each group is too low to draw conclusions, these results suggest that LNG-IUD might achieve a longer response compared to MA, resulting preferable as first line treatment. Further studies are necessary in this regard.

4.2. Strengths and limitations

To the best of our knowledge, this is the third study assessing MMR as predictive markers in conservatively treated AEH and EEC [27,28], and the first adopting hysteroscopic resection. The homogeneity of the study population represents a solid basis to our results. In fact, the study population was only composed by premenopausal patients, who are the main candidates to conservative treatment in the common practice [10,13]. All patients were treated by hysteroscopic resection plus progestins, which likely is the most effective conservative approach available for AEH and EEC [29,30]. The minimal follow-up time required to assess the outcome (*i.e.* 12 months) was achieved in all patients [10,13]. Furthermore, contrary to several previous studies, we only included histologically confirmed AEH and EEC, excluding non-atypical hyperplasia which is a benign functional proliferation [17,22]. MMR-deficient cases were equally distributed between AEH and EEC, limiting the impact of histological diagnosis on the results. Moreover, histological review was performed by two blinded authors for each center in order to improve reliability; this is a crucial point, given the possible pitfalls in the diagnosis of AEH and EEC [2,3] and in the assessment of lymphovascular space invasion, tumor grade and myometrial invasion [45–47].

The main limitations of our study may lie in the retrospective design and the small number of MMR-deficient cases. However, 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 [39]. Moreover, MMR-deficiency in AEH and EEC is much less common than in myoinvasive endometrial carcinoma [27,28,48]. Therefore, it is not easy to adopt a prospective design for this investigation.

5. Conclusion

In women undergoing conservative treatment with hysteroscopic resection plus progestin for AEH or EEC, MMR-deficiency does not appear as a significant predictor of resistance to treatment, but rather as a highly specific predictor of recurrence. This result might be due to the addition of hysteroscopic resection to progestin, which might offer a window period to attempt a pregnancy. However, given the higher risk of recurrence, a closer and more careful follow-up may be necessary in this subset of patients.

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Declaration of Competing Interest

The authors report no conflict of interest.

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