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*Original Research*

# Diagnostic accuracy of hysteroscopy vs dilation and curettage (D&C) for atypical endometrial hyperplasia in patients performing hysterectomy or serial follow-up

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**Abstract**

**Background**: Endometrial hyperplasia (EH) is considered a heterogeneous pre-neoplastic clinical entity characterized by an abnormal glandular proliferation, with less than half of the tissue area occupied by the stroma. The aim of this retrospective study was to evaluate the correlation between the histological diagnosis of atypical endometrial hyperplasia (AEH) obtained through office hysteroscopy (OH) or uterine dilation and curettage (D&C) and the definitive histological evaluation after hysterectomy. **Methods**: Among 112 patients with atypical EH, 45 (40%) underwent hysteroscopy and 67 (60%) curettage. **Results**: The diagnostic accuracy of OH was very high: in particular, it showed a diagnostic coincidence in 87% of cases with the definitive histological diagnosis through hysteroscopy. The curettage, instead, had diagnostic coincidence only in 14% of cases. **Conclusion**: Office hysteroscopy is the ideal procedure for both diagnosis and follow-up of endometrial hyperplasia.

**Keywords:** Endometrial hyperplasia (EH); Office hysteroscopy (OH); Dilation and curettage (D&C); Transvaginal ultrasound (TVUS); Endometrial biopsy (EB); Endometrial carcinoma

## 1. Introduction

Endometrial hyperplasia (EH) is usually detected after investigation of perimenopausal women with abnormal uterine bleeding. It is defined as an excessive proliferation of glands of irregular size and shape with an increase in the glands/stroma ratio [1]. EH is both a precursor and a marker for concurrent endometrial cancer, in particular in the presence of atypia [2]. The incidence of EH differs greatly depending on age and symptoms. In asymptomatic premenopausal women, the incidence of EH without atypia is 5%, while the incidence of EH with atypia is 1% [3]. In premenopausal women with abnormal uterine bleeding, the incidence of EH has been reported to be as high as 10% [4]. In women with PCOS and oligomenorrhea, the reported incidence of EH is 20% [5]. Risk factors for EH seem to be similar to those for endometrial cancer [6]. Most notable among these are increasing body mass index (BMI) and nulliparity. Other risk factors for endometrial carcinoma include chronic anovulation, early menarche, late onset of menopause, and diabetes, impaired inflammatory state [7–9].

Two diagnostic classification systems are used in clinical practice, that differ substantially in their origins and development: The World Health Organization 1994 (WHO 94) classification system and the Endometrial Intraepithelial Neoplasia (EIN) classification system [10–12]. Both the American College of Obstetricians and Gynecologists and the Society of Gynecological Oncology states that endometrial intraepithelial neoplasia (EIN) classification is superior to the WHO94 classification. Despite this, the WHO 94 classification system has been the most used and reported in previously published literature. In 2014 a WHO classification system was introduced by the International Society of Gynecological Pathologists (Table 1, Ref. [12]). This classification divides the hyperplasia into two groups: benign hyperplasia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN). The WHO 2014 schema is more likely to successfully identify precancerous lesions than the WHO 94 classification [13,14].

Pelvic transvaginal ultrasound represents the first level diagnostic test for symptomatic patients [15], nevertheless definitive endometrial hyperplasia (EH) diagnosis is obtained by histological evaluation of specimens obtained in an outpatients' setting during a diagnostic hysteroscopy or a uterine cavity curettage [16,17]. Hysteroscopy is an excellent diagnostic tool for the direct visualization of the uterine cavity [18,19] and is now considered the gold standard for the diagnosis of EH for its elevated sensibility and specificity (95%) [20–22]. The aim of our study was a

**Table 1. WHO 2014 classification of endometrial hyperplasia [12].**

| New term | Synonym | Coexistent invasive endometrial carcinoma |
|---|---|---|
| Hyperplasia without atypia (non-neoplastic) | Benign endometrial hyperplasia; simple non-atypical endometrial hyperplasia; complex non-atypical endometrial hyperplasia; simple endometrial hyperplasia without atypia; complex endometrial hyperplasia without atypia | <1% |
| Atypical hyperplasia (endometrioid intraepithelial neoplasia) (neoplastic) | Complex atypical endometrial hyperplasia; simple atypical endometrial hyperplasia; endometrial intraepithelial neoplasia (EIN) | 25–33%<br>59% |

comparison between the results coming from atypical endometrial hyperplasia (AEH) histological specimens obtained through office hysteroscopy (OH) or uterine dilation and curettage (D&C) and the definitive histological exam after hysterectomy.

## 2. Materials and methods

This is a retrospective study. We collected data from 195 patients with initial diagnosis of EH after endometrial biopsy (EB) during OH or D&C at the Department of Gynecology and Obstetrics, University of Foggia, in the period between January 2003 and December 2016. Among these 195 patients, 83 patients had a diagnosis of EH without cellular atypia and 112 patients EH with atypia. These latter ones, all Caucasian, mainly presented with AUB, sterility, endometrial polyps, and abnormal ultrasound patterns (pre-menopausal endometrial thickness >12 mm or post-menopausal endometrial thickness >5 mm, endometrial hyperechoic area, irregular endometrial lining) (Table 2). For all the patients we collected clinical and pathological characteristics regarding diabetes, HRT, obesity, menopause, tamoxifen therapy and we analyzed anthropometric parameters**.** Clinical features have been described on Table 3. All patients, symptomatic and asymptomatic, had undergone a transvaginal ultrasound (TVUS) before the invasive procedure. Diagnosis of EH was obtained histologically by expert pathologists [23,24]. Hysteroscopy was performed with an operative hysteroscope in office setting with a continuous flow 5 Fr. and an optic scope 2.9 mm (Bettocchi Office Hysteroscope, Karl Storz, Tuttlingen, Germania), through a vaginal approach (without speculum or tenaculum), in absence of anesthesia, but with painkiller treatment to avoid patient's discomfort. Uterine cavity was extended through physiological solution and intrauterine pressure (45 mmHg) was regulated by an electronic system of irrigation (200 mL/min) and aspiration (0.2 bar). Among 112 women diagnosed with atypical endometrial hyperplasia, 80 underwent hysterectomy and were finally included in the statistical analysis. We analyzed the sensitivity, specificity, PPV, NPV, of the histological evaluation of atypical EH obtained by OH or D&C and the definitive histological diagnosis performed after hysterectomy (Table 5). Secondary outcome was then to compare the diagnostic accuracy OH vs D&C. The histological evaluations were all performed according to WHO 2014 classification system. The unpaired Student's $t$ test was used for statistical analysis; $p < 0.05$ was considered statistically significant.

## 3. Results

Among 195 patients with endometrial hyperplasia, 83 were excluded because they did not show atypia. Among 112 patients with atypical EH, 45 (40%) underwent hysteroscopy and 67 (60%) curettage. Among these 112 women, 80 underwent hysterectomy; while among the 32 patients who were not operated, 8 women with mean age of 35 years (25–39) (7.1%) opted for a narrow follow-up by ultrasound every 6 months and hysteroscopy every year, and 10 of them (8.9%) underwent hysteroscopic resection of focal endometrial hyperplastic areas or endometrial polyps placed in atypical hyperplastic areas. Among the 80 women that underwent to hysterectomy, 42 have received the first AEH histological diagnosis by D&C, while 38 received OH. OH sensitivity and specificity data and the comparison with D&C is visible on Tables 4,5,6. Pre-operatory diagnosis was confirmed at definitive histological exam in 39 patients (49%). In 41 cases, diagnosis did not match: 30 women (37.5%) with diagnosis of atypical EH at first bioptic exam, received diagnosis of endometrial carcinoma at the definitive histological exam after hysterectomy; 11 (13.5%) women who underwent to hysterectomy for atypical EH had a benign result at the definitive histologic exam.

Office hysteroscopy biopsy diagnostic accuracy was very high: in particular, diagnosis was coincident between hysteroscopy and definitive histological exam in 87% of cases and only in 14% of cases after curettage (Table 7).

## 4. Discussion

Most of endometrial pathologies show anomalous post-menopausal bleeding, in about 15% of these cases endometrial hyperplasia or endometrial carcinoma is diagnosed [25]. Transvaginal ultrasound (TVUS) is an acceptable alternative to endometrial sampling in some patients and also allows for identification of structural lesions (e.g., polyp, leiomyoma), if present.

**Table 2. Clinical features in patients with AEH.**

| | N | % |
|---|---|---|
| Menometrorragy | 36 | 32.1 |
| AUB post-menopausal | 68 | 60.7 |
| pre-menopausal endometrial thickness >12 mm or post-menopausal endometrial thickness >5 mm | 8 | 7.1 |

**Table 3. Clinical and pathological characteristics in patients with AEH.**

| | n | % |
|---|---|---|
| Age mean | 55.4 | |
| Pre menopausal | 40 | 35.7 |
| Post menopausal | 72 | 64.3 |
| Hormon Replacement Therapy | 26 | 23.2 |
| Nulliparous | 28 | 25.0 |
| Pluriparous | 84 | 75 |
| Overweight (25< BMI <30) | 10 | 8.9 |
| Obesity (>30) | 32 | 28.6 |
| Hypertension | 56 | 50 |
| Diabetes | 32 | 28.6 |
| Tamoxifene assumption | 16 | 14.3 |

**Table 4. EH diagnosis after D&C and confirmation after hysterectomy.**

| | EH diagnosis after D&C | Diagnostic confirmation after hysterectomy |
|---|---|---|
| EH with atypia | 20 | 6 |
| EH without atypia | 22 | 36 |

**Table 5. EH diagnosis after OH and confirmation after hysterectomy.**

| | EH diagnosis after OH | Diagnostic confirmation after hysterectomy |
|---|---|---|
| EH with atypia | 36 | 33 |
| EH without atypia | 2 | 5 |

**Table 6. Sensibility, specificity, PPV and NPV of D&C and OH.**

| | D&C | OH |
|---|---|---|
| Sensibility % | 48 | 95 |
| Specificity % | 81 | 87 |
| PPV % | 77 | 52 |
| NPV % | 38 | 28 |

In postmenopausal patients, ultrasound may demonstrate an increased endometrial thickness with cystic features and heterogeneity; however, ultrasound criteria have not been set for the detection of EH as they have for endometrial carcinoma. Thus, endometrial thickness in a postmenopausal patient in the absence of bleeding is a non-specific finding, but one that requires further evaluation for EH [26].

From our study we can infer that there is an increase of cases of AEH in the last 6 years thanks to an improvement of diagnostic strategies. These data are confirmed also by scientific literature [27]. In our study we have detected that diagnostic coincidence between office hysteroscopy biopsy and hysterectomy was 87%, whilst it was only 14% the coincidence between the curettage "blind samplings" and hysterectomy. With office hysteroscopy we can perform a hysteroscopically-directed endometrial histologic sampling while with D&C we have a blind sampling of the endometrial tissue. Scientific literature confirms that the risk of coexistence of endometroid cancer in patients with AEH is mainly due to the diagnosis obtained using "blinded samples" [28,29]. This risk is reduced when AEH diagnosis is obtained with OH biopsy and even more reduced with a hysteroscopic resection of suspicious lesions observed in hysteroscopy [30,31]. Hysteroscopic endometrial resection should be considered in all patients wherein we can observe an area of EH or endometrial polyps through hysteroscopy, since its diagnostic accuracy is higher than endometrial biopsy [32]. After a pre-operatory diagnosis of AEH, planned surgery can result inadequate (undertreatment) because of the risk of an endometrial cancer, usually diagnosed only after hysterectomy [33–35]. So, histological pre-operatory accuracy is crucial. Although in our study the grade of diagnostic coincidence between the two exams was 45%, (similar to Kurosawa *et al*. [36] with a 45.5% coincidence, Trimble *et al*. [37] or Kisielewski *et al*. [38] with a 47.73% coincidence), the risk of an underlying endometrial carcinoma in patients diagnosed with AEH after biopsy cannot be totally excluded. Cancer was diagnosed in 35.7% of cases in our study, percentage that is confirmed also by GOG study (39.1%) and by other researches (34.09%) [31]. Office hysteroscopy sensitivity is way high as a diagnostic investigation respect to D&C and its accuracy ranges from 85% to 98% in agreement to literature results [19,39–41]. Our study has several limitations. First of all the lack of groups with no hyperplasia who performed hysterectomy and then had a diagnosis of hyperplasia. By including these groups we could have had more specifically the chance to figure out the diagnosis accuracy. Also we are aware of the risk of missed diagnosis on pathology at the time of hys-

**Table 7. Diagnostic accuracy between EB in OH and D&C and definitive histological exam.**

| Women undergo to | Total | Confirmed Diagnoses | % |
|---|---|---|---|
| Hysteroscopy | 38 | 33 | 87 |
| D&C | 42 | 6 | 14 |

terectomy. In our study 37.5% of women with diagnosis of atypical EH at first bioptic exam, had definitive diagnosis of endometrial carcinoma, 13.5% had a benign result at the definitive histologic exam. These percentages are in line with the current literature [42,43].

Among the other limitations of our study we can include the relatively small number of the sample and the retrospective pattern. This study was performed in only one hospital and all the procedures were performed by different hysteroscopists. This could be another important bias because hysteroscopic experience is crucial in a so difficult diagnosis like atypical endometrial hyperplasia.

Also, the level of discrepancy between histological pre–operatory and post–hysterectomy specimens is evident because of insufficient information obtained from endometrial uterine cavity inadequate samples.

## 5. Conclusions

The high diagnostic accuracy of office hysteroscopy renders hysteroscopy the ideal procedure for both diagnosis and follow-up of endometrial hyperplasia. Hysteroscopy enables direct visualization and controlled operator movements with a lower risk of perforation, as no sounding or cervical dilatation is performed [44]. Moreover, it is most of the time a well-tolerated procedure, thus avoiding general anesthesia, and decreasing the costs [45].

## Author contributions

Conceptualization—FS, FG, PG and LN; writing—original draft—FS, LN, SA, GS, FG, MND and VDF; writing—review and editing—FS, SA, MND, GS and FG; supervision—LN, SA and PG. All authors have read and agreed to the published version of the manuscript.

## Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki ethical standards. Informed consents were taken from study participants. The authors declare that ethical review and approval were waived for this study, due to retrospective design.


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## Conflict of interest

The authors declare no conflict of interest.

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