Review Article

Sampling in Atypical Endometrial Hyperplasia: Which Method Results in the Lowest Underestimation of Endometrial Cancer? A Systematic Review and Meta-analysis

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ABSTRACT

Our objective was to identify the most accurate method of endometrial sampling for the diagnosis of complex atypical hyperplasia (CAH), and the related risk of underestimation of endometrial cancer. We conducted a systematic literature search in PubMed and EMBASE (January 1999–September 2013) to identify all registered articles on this subject. Studies were selected with a 2-step method. First, titles and abstracts were analyzed by 2 reviewers, and 69 relevant articles were selected for full reading. Then, the full articles were evaluated to determine whether full inclusion criteria were met. We selected 27 studies, taking into consideration the comparison between histology of endometrial hyperplasia obtained by diagnostic tests of interest (uterine curettage, hysteroscopically guided biopsy, or hysteroscopic endometrial resection) and subsequent results of hysterectomy. Analysis of the studies reviewed focused on 1106 patients with a preoperative diagnosis of atypical endometrial hyperplasia. The mean risk of finding endometrial cancer at hysterectomy after atypical endometrial hyperplasia diagnosed by uterine curettage was 32.7% (95% confidence interval [CI], 26.2–39.9), with a risk of 45.3% (95% CI, 32.8–58.5) after hysteroscopically guided biopsy and 5.8% (95% CI, 0.8–31.7) after hysteroscopic resection. In total, the risk of underestimation of endometrial cancer reaches a very high rate in patients with CAH using the classic method of evaluation (i.e., uterine curettage or hysteroscopically guided biopsy). This rate of underdiagnosed endometrial cancer leads to the risk of inappropriate surgical procedures (31.7% of tubal conservation in the data available and no abdominal exploration in 24.6% of the cases). Hysteroscopic resection seems to reduce the risk of underdiagnosed endometrial cancer. Journal of Minimally Invasive Gynecology (2016) 23, 692–701

Keywords: Endometrial cancer; Endometrial sampling; Hysteroscopy

Endometrial hyperplasia 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].

As shown in previous studies, these lesions may coexist with endometrial cancer (EC) at the time of diagnosis in 43% to 50% of cases [2,3]; however, they may also progress to it. The risk of endometrial hyperplasia progressing to carcinoma is related to the presence and severity of cytologic atypia [4]. It has been shown that progression to carcinoma occurs in 1% of patients with simple hyperplasia, 3% of patients with complex hyperplasia, 8% of patients with atypical simple hyperplasia, and 29% of patients with atypical complex hyperplasia [5]. Failure to evaluate precisely patients with endometrial hyperplasia can result in undertreatment; although endometrial hyperplasia can be treated successfully with progestins or medical therapy, hysterectomy is recommended for postmenopausal women with cytologic atypia [1].

It is not yet known which is the most accurate method to obtain histologic samples; for many years, dilatation and curettage (D&C) has been the method of choice for diagnosing endometrial pathology in women with abnormal
uterine bleeding. However, in 60% of the curettage procedures, less than half of the uterine cavity is curetted, thereby calling the accuracy of this method into question [6]. Moreover, the whole or parts of the focal lesion may remain in the uterine cavity after D&C in 87% of women with focally growing lesions [7].

Some authors stress the high accuracy of hysteroscopy for distinguishing between a normal and an abnormal endometrium thanks to the advantages of high magnification for direct visualization of the uterine cavity and the possibilities of targeted biopsies [8].

Methods

This review was conducted in order to understand the risk of coexisting EC in patients with a diagnosis of complex atypical hyperplasia (CAH) by endometrial biopsy, taking into account the method used to do this (i.e., direct biopsy during hysteroscopy, endometrial hysteroscopic resection, or D&C of the uterine cavity). We decided to not consider different forms of atypical endometrial hyperplasia (simple and complex hyperplasia) because those data were missing in most articles, and, furthermore, the histologic diagnosis is difficult and controversial.

Studies about Pipelle were not included in our review because we decided to focus on the 3 sampling methods that seemed the most reliable to us [9,10]. Furthermore, there is a minority of studies comparing Pipelle and a real gold standard such as hysterectomy. The majority of studies included only patients who had undergone D&C as the reference. Even if this method is probably the most common method of endometrial sampling for abnormal uterine bleeding or postmenopausal bleeding, office biopsy may be insufficient to detect endometrial disease because blind techniques of sampling are not indicated for focal anomalies. The nonrepresentative nature of these blind procedures may be related to the small proportion of the endometrial surface sampled [10].

Literature Search

A computerized search in PubMed and EMBASE was performed to identify all registered articles on this subject published between January 1999 and September 2013 restricted to English, French, Italian, or Spanish languages. We used the following subsets of search terms combined by the word “and”: “hysteroscopy,” “curettage,” “endometrial resection,” “endometrial hyperplasia,” “endometrial cancer,” and “hysterectomy.” In addition, cross-references of all selected articles were checked.

Study Selection

The review focused on studies (clinical trials, comparative studies, controlled clinical trials, randomized controlled trials, and multicenter studies) in which the results of the diagnostic test of interest were compared with the results of a reference standard.

The population of interest was premenopausal and postmenopausal women submitted to endometrial sampling because of a suspicion of endometrial disease (with or without symptoms) with a diagnosis of atypical endometrial hyperplasia and who underwent hysterectomy. We excluded populations consisting entirely of patients treated by tamoxifen or affected by familiar diseases (i.e., HNPCC [Hereditary Non-Polyposis Colorectal Cancer] syndrome) because of the different prevalence of EC in this population influencing outcome measures. We also excluded studies in which the histologic findings were not compared with the reference standard (i.e., hysterectomy), the sampling methods were different from the 3 diagnostic tests, and hysterectomy was realized for other indications.

The diagnostic tests were uterine curettage (group 1), hysteroscopically guided biopsy (group 2), and endometrial hysteroscopic resection (group 3), and the reference standard was hysterectomy. The primary outcome measure was the percentage of unexpected cancer cases diagnosed at hysterectomy and missed during endometrial sampling (endometrial sampling with histologic diagnosis of atypical endometrial hyperplasia).

In some studies, other techniques of endometrial sampling (i.e., Pipelle, Vabra, or others) were performed along with curettage, hysteroscopically guided biopsy, or hysteroscopic endometrial resection. In these cases, we included only the population submitted to the reference test.

When the histopathology results were described very precisely, data were recorded in “simplified” histologic groups including “atypical endometrial hyperplasia,” “nonatypical endometrial hyperplasia,” and “others” (including polyps, atrophic endometrium, and proliferative or secretory endometrium).

Finally, for each study and for all of them, the percentage of endometrial sampling results that failed to detect the correct diagnosis of EC was calculated. The surgical procedure to perform the hysterectomy was recorded when specified.

The search resulted in 1938 PubMed abstracts (Fig. 1); 2 reviewers read those abstracts and titles, and, of these, 69 relevant articles were selected for full reading. The full articles of these examples were then evaluated by 2 reviewers to determine whether full inclusion criteria were met.

In total, 42 studies were excluded because of various reasons including reference standard different from hysterectomy [7,11–15], use of hysteroscopy without biopsy [16] or endometrial biopsy without previous hysteroscopy [17–20], use of curetting methods different from the standard (i.e., D&C) [21,22], inclusion of patients submitted to hysterectomy for a diagnosis other than endometrial hyperplasia (i.e., EC and carcinoma in situ) [23–27], correlation between specific histology group and hysterectomy not available [28–31], more complete data in a subsequent article [32], and use of several sampling tests without taking them separately [33,34].
A total of 27 studies were finally included in our review, with agreement of the 2 reviewers. For each study, the 2 reviewers recorded the sampling technique, the histologic result of endometrial sampling, and the number of ECs diagnosed at hysterectomy. We also analyzed the characteristics of the population (premenopausal or postmenopausal, the mean population age with standard deviation, and range when present). The data were recorded in an electronic database.

A total of 1106 patients with a preoperative diagnosis of atypical endometrial hyperplasia were included in our review. Twenty-two of the 27 studies compared uterine curettage with hysterectomy [35–47], 6 compared histology obtained by hysteroscopically guided biopsy with hysterectomy [45,48–52], and 3 studies compared histology obtained by endometrial hysteroscopic resection with hysterectomy [45,48,53]. Characteristics of studies are summarized in Table 1. Most of the studies included pre- and postmenopausal subjects. Two studies had a postmenopausal population only [12,39], and 5 articles did not specify menopausal status [38,42,47,51,54].

Fifteen studies included patients given hysterectomy based exclusively on a previous diagnosis of atypical hyperplasia [35,38,41–43,45,48,50–57]. The remaining studies distinguished among different histologic diagnoses (such as simple hyperplasia with and without atypia, complex hyperplasia with and without atypia, endometrial polyps, and dysfunctional endometrium) [36,37,39,40,44,46,47,49,58–61]. In this category, most of the time surgical indications included abnormal uterine bleeding [36,37,39,40,44,47,49,58–61], but leiomyoma [46,49], endometriosis [46], adenomyosis [61], cervical polyps, and abnormal endometrial thickness in menopause [49] were also included.

Three studies considered repeated tests on the same patients, performing a “multistep” preoperative diagnosis. In these studies, we considered only the results obtained by the diagnostic test of interest.

![Statistical Analysis](https://example.com/statistical-analysis)

**Statistical Analysis**

Comprehensive meta-analysis software [62] was used to conduct random-effects meta-analyses. Heterogeneity in the study results was evaluated by examining forest plots and confidence intervals and by using formal tests for homogeneity based on the I² statistics. A forest plot graph is presented in Figure 2. Heterogeneity was quantified by I² [63]. Publication bias was assessed by a funnel plot (Fig. 3); in this figure, each dot represents a study, and each symbol represents a group. Thus,
a sensitivity analysis was conducted to assess the influence on the global effect size of the inclusion and exclusion of some studies.

For appraisal of the methodologic quality of the studies, we used the Canadian Task Force classification, a measurement tool to assess the methodologic quality

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Total no. of patients in the study</th>
<th>No. of patients submitted to tests of interest</th>
<th>Type of test of interest</th>
<th>Symptoms</th>
<th>Mean age ± SD (range)</th>
<th>Canadian Task Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whyte et al, 2010</td>
<td>Pre- and postmenopausal</td>
<td>88</td>
<td>51</td>
<td>D&amp;C</td>
<td>NS</td>
<td>53.9 (37–85)</td>
<td>II-2</td>
</tr>
<tr>
<td>Chen et al, 2009</td>
<td>Pre- and postmenopausal</td>
<td>77</td>
<td>77</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>49.6</td>
<td>II-2</td>
</tr>
<tr>
<td>Obeidat et al, 2009</td>
<td>Pre- and postmenopausal</td>
<td>55</td>
<td>55</td>
<td>D&amp;C</td>
<td>NS</td>
<td>51.8 (35–74)</td>
<td>II-2</td>
</tr>
<tr>
<td>Sub-Burgmann et al, 2009</td>
<td>NS</td>
<td>824</td>
<td>193</td>
<td>D&amp;C</td>
<td>NS</td>
<td>56 (27–85)</td>
<td>II-2</td>
</tr>
<tr>
<td>Edris et al, 2007</td>
<td>Pre- and postmenopausal</td>
<td>22</td>
<td>4</td>
<td>HSC-res</td>
<td>AUB</td>
<td>55.5 (46–78)</td>
<td>II-3</td>
</tr>
<tr>
<td>Garuti et al, 2006</td>
<td>Post-menopausal</td>
<td>28</td>
<td>25</td>
<td>HSC-bio</td>
<td>AUB/increased endometrial thickness</td>
<td>61 ± 6.1</td>
<td>II-3</td>
</tr>
<tr>
<td>Saygili et al, 2006</td>
<td>NS</td>
<td>42</td>
<td>42</td>
<td>D&amp;C</td>
<td>AUB/increased endometrial thickness</td>
<td>NS</td>
<td>II-3</td>
</tr>
<tr>
<td>Karamursel et al, 2005</td>
<td>Pre- and postmenopausal</td>
<td>204</td>
<td>204</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>57.4 ± 9.3 (28–87)</td>
<td>II-2</td>
</tr>
<tr>
<td>Merisio et al, 2005</td>
<td>Pre- and postmenopausal</td>
<td>70</td>
<td>39</td>
<td>D&amp;C</td>
<td>NS</td>
<td>55.51 ± 11.9 (38–30)</td>
<td>II-3</td>
</tr>
<tr>
<td>Shutter et al, 2005</td>
<td>NS</td>
<td>60</td>
<td>30</td>
<td>D&amp;C</td>
<td>NS</td>
<td>48.9 ± 8.3</td>
<td>II-2</td>
</tr>
<tr>
<td>Bilgin et al, 2004</td>
<td>Pre- and postmenopausal</td>
<td>46</td>
<td>38</td>
<td>D&amp;C</td>
<td>NS</td>
<td>53.4 (45–76)</td>
<td>II-3</td>
</tr>
<tr>
<td>Gundem et al, 2003</td>
<td>Pre- and postmenopausal</td>
<td>103</td>
<td>103</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>52 (30–83)</td>
<td>II-3</td>
</tr>
<tr>
<td>Ceci et al, 2002</td>
<td>Pre- and postmenopausal</td>
<td>443</td>
<td>443</td>
<td>HSC-bio</td>
<td>AUB/increased endometrial thickness</td>
<td>52</td>
<td>II-2</td>
</tr>
<tr>
<td>Xie et al, 2002</td>
<td>Pre- and postmenopausal</td>
<td>150</td>
<td>150</td>
<td>D&amp;C</td>
<td>NS</td>
<td>48.5 (31–76)</td>
<td>II-2</td>
</tr>
<tr>
<td>Bettocchi et al, 2001</td>
<td>NS</td>
<td>397</td>
<td>397</td>
<td>D&amp;C</td>
<td>AUB/endometrial polyp</td>
<td>43</td>
<td>II-2</td>
</tr>
<tr>
<td>Leitao Jr. et al, 2010</td>
<td>Pre- and postmenopausal</td>
<td>197</td>
<td>123</td>
<td>D&amp;C</td>
<td>NS</td>
<td>54 (32–86)</td>
<td>II-2</td>
</tr>
<tr>
<td>Yarandi et al, 2010</td>
<td>Pre- and postmenopausal</td>
<td>311</td>
<td>311</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>46.6 (30–86)</td>
<td>II-2</td>
</tr>
<tr>
<td>Daud et al, 2011</td>
<td>Pre- and postmenopausal</td>
<td>280</td>
<td>220</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>55.7 ± 11.4</td>
<td>II-2</td>
</tr>
<tr>
<td>Kurosawa et al, 2012</td>
<td>Pre- and postmenopausal</td>
<td>22</td>
<td>22</td>
<td>HSC-bio</td>
<td>NS</td>
<td>53.4</td>
<td>II-2</td>
</tr>
<tr>
<td>Demirkiran et al, 2012</td>
<td>Pre- and postmenopausal</td>
<td>673</td>
<td>161</td>
<td>D&amp;C</td>
<td>AUB/increased endometrial thickness</td>
<td>45.3 (27–86)</td>
<td>II-2</td>
</tr>
<tr>
<td>Barut et al, 2012</td>
<td>Pre- and postmenopausal</td>
<td>645</td>
<td>645</td>
<td>D&amp;C</td>
<td>NS</td>
<td>50.9 (23–81)</td>
<td>II-2</td>
</tr>
<tr>
<td>Saleh et al, 2012</td>
<td>Pre- and postmenopausal</td>
<td>137</td>
<td>93</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>49.1 (35–76)</td>
<td>II-2</td>
</tr>
<tr>
<td>Kurt et al, 2011</td>
<td>Pre- and postmenopausal</td>
<td>58</td>
<td>58</td>
<td>D&amp;C</td>
<td>AUB</td>
<td>51.7 ± 9.2</td>
<td>II-3</td>
</tr>
<tr>
<td>Robbe et al, 2012</td>
<td>NS</td>
<td>39</td>
<td>29</td>
<td>D&amp;C</td>
<td>NS</td>
<td>60.4 (34–90)</td>
<td>II-3</td>
</tr>
</tbody>
</table>

AUB = abnormal uterine bleeding; D&C = dilatation and curettage; HSC-bio = hysteroscopically guided biopsy; HSC-res = endometrial hysteroscopic resection; NS = not specified; SD = standard deviation.
of studies (Table 1). Most of the studies included were classified II-2 (n = 19/27) (i.e., evidence obtained from well-designed cohort or case-control studies), and 8 were classified II-3 (i.e., evidence obtained from several timed series with or without the intervention). All studies included were retrospective, and subjects were always included when they had a preoperative diagnosis of atypical endometrial hyperplasia followed by hysterectomy with pathological analysis.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk of undiagnosed endometrial cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: D&amp;C</td>
<td>32.7% (CI 95% [26.2–39.9])</td>
</tr>
<tr>
<td>II: HSC-bio</td>
<td>45.3% (CI 95% [32.8–58.5])</td>
</tr>
<tr>
<td>III: HSC-res</td>
<td>5.8% (CI 95% [0.8–31.7])</td>
</tr>
</tbody>
</table>

CI = confidence interval; D&C = dilatation and curettage; HSC-bio = hysteroscopically guided biopsy; HSC-res = endometrial hysteroscopic resection.

Global omnibus p value: p = .043.
Results

The total number of patients with a preoperative diagnosis of atypical endometrial hyperplasia based on curettage (group 1) was 984; of these 984 cases, 296 were diagnosed to have EC at hysterectomy (30.1%), varying from 0% to 66.6%. Using the random-effects model, the risk of having undiagnosed EC after D&C for atypical endometrial hyperplasia was 32.7% (95% confidence interval [CI], 26.2–39.9).

The total number of patients with a preoperative diagnosis of atypical endometrial hyperplasia based on hysteroscopically guided biopsy (group 2) was 99. EC was diagnosed at hysterectomy in 46 patients (46.5%), and the result using the random-effects model was 45.3% (95% CI, 32.8–58.5).

The number of patients submitted to endometrial resection with a diagnosis of atypical endometrial hyperplasia (group 3) was 23; of these 23, only 1 had EC at hysterectomy (4.3%), resulting in 5.8% (95% CI, 0.8–31.7) with the random-effects model.

Between the 3 techniques, there was a significant difference (global p value = .043). This difference stayed significant between groups 3 and 2 (p = .03) but became nonsignificant between the other groups (p = .06 and p = .21) because of the heterogeneity of the groups. However, there was a significant trend between endometrial resection and the 2 other groups (Table 2).

Only 8 articles specified the surgical approach, including 369 hysterectomies. Of these, 231 were abdominal hysterectomies (134 with bilateral salpingo-oophorectomy [BSO] [36.3%] and 97 without BSO [26.3%]), 91 were vaginal hysterectomies (71 with BSO [19.2%] and 20 without BSO [5.4%]), 7 were laparoscopic assisted with BSO (1.9%), and 40 were laparoscopic hysterectomies with BSO (10.8%) [35,41,45,50,52,53,56]. In total, 117 hysterectomies were realized without BSO (31.7%) and 91 without abdominal exploration (24.6%). Of the hysterectomies performed without BSO or abdominal exploration, the number of ECs was not specified at the time of the intraoperative assessment.

Discussion

The most accurate and reliable method of endometrial sampling when endometrial disease is suspected is not yet established, so several methods of endometrial sampling are commonly used. If the most accurate procedure were known, the incidence of missed ECs would be reduced significantly, resulting in optimal clinical management of patients diagnosed with endometrial hyperplasia.

Main Findings

In our study, we performed the first meta-analysis to investigate the correlation of hysteroscopically guided biopsy, hysteroscopic endometrial resection, and uterine curettage to the presence of EC on hysterectomy. In our study, the risk of underestimation of EC seemed to be higher when a diagnosis of atypical endometrial hyperplasia was made with uterine curettage and hysteroscopically guided biopsy compared with resection. These results need to be confirmed by larger studies.

Comparison Between Hysteroscopic Techniques of Endometrial Sampling and Uterine Curettage

The literature is lacking in studies focused on the comparison between hysteroscopy and curettage for the diagnosis of atypical endometrial hyperplasia, whereas a number of studies compare other sampling methods (mainly D&C and Pipelle). Three studies were found comparing D&C with hysteroscopically guided biopsy in perimenopausal women [49,51,64]. In the first, the authors found that hysteroscopy with directed biopsy was more effective than D&C for collecting endometrial samples adequate for histologic examination in all types of uterine lesions [64] (N = 734). In the second, hysteroscopy demonstrated a greater diagnostic accuracy than D&C, showing a statistically significant difference in the sensitivity and the negative predictive value for benign and malignant endometrial pathologies [49] (N = 443). Conversely, in the third study [51], the results indicated a greater reliability of D&C compared with hysteroscopically guided biopsy for the number of cases of underdiagnosed EC (N = 126).

Complications of sampling procedures were not reported or discussed in any of the articles. However, we know that hysteroscopic resection may have a higher incidence of complications (e.g., fluid overload). Furthermore, hysteroscopic resection is a more invasive procedure, and there is a real learning curve for improvement in performing hysteroscopic resection.

The techniques are slightly different: most of the time hysteroscopic resection requires patient hospitalization and anesthetic study and, during the procedure, dilatation of the cervix and use of distension medium. Conversely, direct endometrial biopsy can be performed by hysteroscopy in an outpatient office setting with less exposure time. Furthermore, a pathological study is shorter because the amount of endometrial tissue to analyze is smaller. All this shortens the time to definitive intervention with less cost. However, in our study, we did not focus on financial differences between those different sampling methods.

Role of Office Biopsy in the Detection of Endometrial Hyperplasia

The literature is rich in studies about the efficacy of blind biopsy (“office biopsy”) in diagnosing endometrial disease (cancer and hyperplasia). One meta-analysis including 7914 pre- and postmenopausal women compared endometrial biopsies obtained by different devices (Pipelle, Vabra, Novak, and others) with histologic findings obtained by D&C, hysterectomy, or both. The results showed that endometrial biopsy with Pipelle is better than other endometrial techniques
(Vabra, Novak, and others) in the detection of EC and atypical hyperplasia [20] (detection rate of 99.6% in postmenopausal women and 91% in premenopausal women). In this study, only a minority of the studies included patients who had a true gold standard (hysterectomy) (n = 2130, 26.9%), whereas the majority of studies included only patients who had undergone D&C as the reference (n = 3622, 45.8%). The others studies included patients who underwent hysterectomy, D&C, or hysteroscopy without distinction. In recent years, several publications have reported that the accuracy of D&C is limited because in 60% of the curettage procedures less than half of the uterine cavity is curetted [8]. In this meta-analysis, they did not perform a separate analysis for studies that used either hysterec-
tomy or D&C as the reference. Those results of detection of endometrial carcinoma and atypical hyperplasia with Pipelle are not suitable because D&C should not be used as a reference because of the high risk of undiagnosed endometrial carci-
noma. (In our study, the risk of having undiagnosed EC after D&C for atypical endometrial hyperplasia was 32.7%).

Furthermore, office biopsy may be insufficient to detect endometrial disease because blind techniques of sampling are not indicated for focal anomalies. The nonrepresentative nature of these blind procedures may be related to the small proportion of the endometrial surface sampled [65].

This observation was confirmed by the review conducted by Clark et al in 2001 [19]. Studies were selected if the accuracy of outpatient endometrial biopsy, in women with abnormal pre- or postmenopausal uterine bleeding, was estimated compared with a reference standard, which was endo-
metrial histology obtained by tissue sampling under anesthesia. The review included 881 women. The results show that endometrial biopsy alone has modest overall accuracy in diagnosing endometrial hyperplasia and is only moderately useful in informing clinical decision making. Therefore, additional endometrial assessment with outpatient hysteroscopy and/or transvaginal ultrasonography should be undertaken.

Similarly, transvaginal ultrasonography could be impor-
tant and should be evaluated. In our work, 2 studies [52,60] evaluated the interest of ultrasound, measuring endometrial thickness. It is known that most endometrial pathologies are associated with a thickened endometrium. In the first study [52], ultrasound was performed after endo-
metrial sampling and before surgery. No significant differ-
ence was found between patients with CAH and those with a final diagnosis of endometrial carcinoma at hysterectomy. In the second study [60], no statistically significant effect of endometrial thickness was shown on biopsy results because it allows a large number of cases of abnormal uterine bleeding to be diagnosed (e.g., polyps).

**Role of Operative Hysteroscopy in the Diagnosis of Endometrial Hyperplasia**

Hysteroscopic endometrial resection has a particular place among other techniques of endometrial sampling. The total number of patients included in group 3 was small (n = 23). Out of 3 studies, only 4 and 2 cases [45,53] were included in 2 studies, with no cancer diagnosed in subsequent hysterectomy. The percentage of unexpected cancer after hysteroscopic resection (group 3) seems to be lower than observed in other groups (groups 1 and 2), even if it is only a significant trend, and this could be related to the technique itself. In fact, in hysteroscopic resection, most of the endometrium is removed, unlike the other 2 techniques when only endometrial sampling is performed. There are no specific hysteroscopic signs of malignancy, and between groups 2 and 3, the benefit of resection could be caused only by the completeness of the sample.

In total, according to our results, hysteroscopic resection seems to be a complete and reliable analysis, but these hypotheses need to be confirmed by other studies, especially because these results were obtained with a small number of patients. Hysteroscopic resection seems to be a safe method of endometrial sampling, albeit more expensive, but the initial investment is probably justified in terms of improved screening and therefore profits over the long-term.

**Complexity of Histologic Diagnosis of Atypical Endometrial Hyperplasia**

Only 1 article considered different forms of atypical endometrial hyperplasia [51]; of the 126 patients who under-
went hysterectomy for preoperative diagnosis of CAH, 24 patients were diagnosed with simple CAH (19%) and 102 patients (81%) with complex CAH. There were no patients with endometrial carcinoma after hysterectomy among the patients who carried a preoperative diagnosis of complex CAH. The high rate of misdiagnosed cancer among patients diagnosed with CAH may be related in part to the fact that this diagnosis is often controversial and difficult to make, even for expert pathologists. The rate of agreement among 3 expert pathologists on 306 endometrial samples identified as CAH was 38%, whereas they suggested in 29% of cases a more severe diagnosis and in 25% a less severe diagnosis [65]. In another study, the mean percentage of agreement was lowest for complex hyperplasia and for atypical hyperplasia in the diagnosis of 56 endometrial specimens by 5 Eu-
ropean expert gynecologic pathologists using the World Health Organization classification. The authors suggested that the lack of agreement and reproducibility in the recog-
nition of the histologic feature of stromal alterations to differentiate atypical hyperplasia from well-differentiated adenocarcinoma involves an evolution in the histologic classification. This should be simplified by including a combi-
ined category for simple and complex hyperplasia called hyperplasia and a combined category for atypical hyperplas-
ia and well-differentiated adenocarcinoma called endome-
triod hyperplasia [66]. In our study, we decided not to consider different forms of atypical endometrial hyperplasia because of that complexity of histologic diagnosis. Further-
more, data were missing in most articles.
It should be noted that there is a new nomenclature that now refers to atypical endometrial hyperplasia as “endometrial intraepithelial neoplasia.” In our study, we decided not to use this new nomenclature because in the studies included the endometrial pathology is called atypical endometrial hyperplasia.

**Surgical Management of Patients With Atypical Endometrial Hyperplasia**

Knowledge of the risk of underestimating EC is important for subsequent clinical management. A cancer diagnosis should lead to preoperative staging (i.e., magnetic resonance imaging), which should be performed to exclude overt myometrial invasion and cervical or adnexal involvement. Expert ultrasound can be considered as an alternative (level of evidence: III, strength of recommendation: B) [67,68]. This can also lead to a different surgical approach (laparotomy or laparoscopy route) and procedure (BSO, abdominal exploration, lymph node dissection, etc.); a specialized gynecologic oncologist should perform surgery if it is cancer. During hysterectomy for CAH, intraoperative frozen section may be performed to determine the presence of EC and the depth of tumor invasion. Nevertheless, some authors suggest poor reliability of this test for the detection of invasive disease [69], reconsidering comprehensive surgical staging after the diagnosis of CAH like in EC [35]. In a recent multicenter prospective cohort study (Gynecologic Oncology Group no. 167), Trimble et al [30] reported that 42.6% (123/289) of women undergoing hysterectomy for definitive management of CAH had endometrial carcinoma in their hysterectomy specimens and that although the great majority of the tumors were grade 1, 6 tumors were grade 2, and 2 tumors were grade 3. Of the carcinomas identified, 105 of 123 tumors (85.4%) were stage IA considering Fédération Internationale de Gynécologie et d’Obstétrique classification 2009; 13 (10.6%) were IB (myoinvasive involved the outer 50% of the myometrium). For 5 tumors, there was no stage classification [30].

In the presence of myometrial infiltration, the risk of lymph node infiltration exists, and lymphadenectomy should be discussed [35]. In our study, only 8 articles specified the surgical approach. Of the 369 hysterectomies, 117 were performed without BSO (97 abdominal hysterectomies and 20 vaginal hysterectomies). All the laparoscopic or laparoscopic hysterectomies were performed with BSO. With the rate of underestimated EC after D&C or hysteroscopically guided biopsy, the surgical procedure should systematically respect oncologic rules. During hysterectomy, BSO and abdominal evaluation should at least be discussed. The fact that 117 hysterectomies were performed without BSO (31.7%) and 91 without abdominal exploration (24.6%) is questionable with respect to the oncologic rules (10.6% of undiagnosed cancers were finally stage IB [30]). Despite this, at the moment, laparoscopy seems to be the less used surgical method to perform hysterectomy with BSO in patients with CAH.

Finally, the safety of hysteroscopy in cases of EC should be discussed. A recent meta-analysis, including 9 trials for a total of 1015 patients, suggested that diagnostic hysteroscopy in women with EC results in statistically significant higher endometrial cell seeding in the peritoneal cavity and statistically significant higher tumor upstaging in patients with disease limited to the uterus compared with no hysteroscopy (D&C, biopsy, or no diagnostic test before hysterectomy) [68]. The degree of tumor cell dissemination is increased by isotonic sodium chloride as the distension medium and when high levels of inflated media pressure are reached (100 mm Hg). Nevertheless, the prognostic significance of positive peritoneal cytology after diagnostic hysteroscopy is unclear. Furthermore, in their study, Ben-Arie et al [70] compared the outcome measures of patients (N = 392) with endometrial adenocarcinoma diagnosed by endometrial biopsy, uterine curettage, or hysteroscopy. They showed no statistically significant difference in the survival rate or recurrence rate between the different diagnostic methods applied [70]. Consequently, hysteroscopy can be safely used in case of EC suspicion.

Globally, with the risk of underestimated EC, the surgical procedure should systematically respect oncologic rules, so BSO and an abdominal evaluation should be associated during the same surgical procedure.

**Strengths and Weaknesses of the Review**

The methodologic quality of the included studies was analyzed using the Canadian Task Force classification, with most of the studies assessed as not being of high quality. A limitation of this review is the heterogeneity of populations and groups, which may impact the generalizability of the findings. There are 22 studies (n = 984 patients) in group 1, 6 in group 2 (n = 99), and only 3 in group 3 (n = 23). This difference causes a high heterogeneity (total I² = 67.8 with I² = 72.0 for group 1, I² = 30.6 for group 2, and I² = 0.0 for group 3). However, we used a random-effects analysis to take account of this heterogeneity, and the results indicated a statistically significant difference.

**Conclusion**

A review of the literature shows that hysteroscopically guided biopsy and uterine curettage may have a high risk of underestimation of EC, and this rate of underdiagnosed EC could lead to inappropriate surgical procedures. Hysteroscopic endometrial resection seems to lower this risk. However, this review highlights the need for a larger amount of data to confirm this observation, and the standard approach for evaluation of the uterine cavity could change in favor of operative hysteroscopic techniques, especially in cases of women at risk of serious endometrial disease.
References


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