Concordance between hysteroscopic impression and endometrial histopathological diagnosis

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CONCORDANCE BETWEEN HYSTEROSCOPI C IMPRESSION AND ENDOMETRIAL HISTOPATHOLOGICAL DIAGNOSIS

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Objective: To evaluate the accuracy of hysteroscopic impression for diagnosing benign and malignant endometrial pathology.

Method: A retrospective cross-sectional study involving case records of 412 patients who underwent hysteroscopy with diagnostic dilatation and curettage (D&C) at University Malaya Medical Centre from January 2009 to August 2011, and cases with records of previous hysteroscopies (2007-2008). Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values; likelihood ratios (LR) and post-test probabilities of hysteroscopy were calculated. D&C was set as the ‘gold standard’.

Results: Hysteroscopy and histology results were concordant in 366(88.8%) subjects. Sensitivity, specificity, PPV and NPV were high exceeding 80%. Moderate sensitivity for endometrial hyperplasia (64.4%, 95% CI=49.8%-76.8%) with moderate PPV for malignancy (62.1%, 95% CI=44.0%-77.3%) due to misdiagnosing hyperplasia as malignancy. PPV for leiomyoma was reduced (83.3%, 95% CI=60.8%-94.2%) despite 100% sensitivity, due to D&C false negatives. High positive LR (>10) and low negative LR (<0.2) was observed generally except for endometrial hyperplasia (0.36). Hysteroscopy had moderate positive post-test probability for malignancy (0.62) but effective in ruling out malignancy (negative post-test probability=0.00).

Conclusion: Hysteroscopy is accurate for focal and malignant endometrial pathology but only moderate for hyperplasia. Endometrial sampling is recommended for all cases especially when suspecting hyperplasia or malignancy.

Keywords: abnormal uterine bleeding, dilatation and curettage, histopathology, hysteroscopy
Introduction

Abnormal uterine bleeding accounts for 25% to 50% of gynecology clinic visits. This may include pre-malignant endometrial hyperplasia, or carcinoma. (Bradley, 2011) Endometrial carcinoma is the sixth commonest malignancy among Malaysian females with an age adjusted incidence rate of 4.1 per 100,000 women. (National Cancer Registry Report, 2011) Thus, investigation to detect such pathology especially in the pre-malignant state is crucial. Direct visualization of the uterus was reputed to be a safe and accurate diagnostic model.(Seamark, 1998) Diagnostic hysteroscopy with endometrial biopsy is currently the ‘gold standard’ of diagnosing endometrial pathology. However, there is ongoing debate on the feasibility of hysteroscopy as a one-stop diagnosis; while studies still suggest that subsequent histological diagnosis is inevitably necessary through the routine curettage.(Tabata et al., 2001)

Therefore, this study was undertaken to assess the performance of hysteroscopy as compared to the conventional curettage. The aim was to evaluate the sensitivity, specificity, positive and negative predictive values of hysteroscopic impression in diagnosing normal and pathological endometrium.

Methods

This is a retrospective cross-sectional study utilizing case files of all women who underwent hysteroscopy with diagnostic dilatation and curettage (D&C) in University of Malaya Medical Centre (UMMC) between 1st January 2009 and 31st August 2011. Patients who have undergone hysteroscopy elsewhere and subsequently referred to UMMC for histopathology interpretation were excluded.

A total of 588 patients were identified from the Operating Theatre registry. A total of 485 case folders were successfully traced at the Records Department. There were 15 cases with additional procedures performed between 1st January 2007 and 31st December 2008 which were also included. After excluding 88 cases with incomplete or inconclusive data, a total of 412 cases were included in data analysis. Those excluded cases were 54 hysteroscopic
impressions reported as “fluffy endometrium”, inadequate sampling in 32 cases; and 2 failed hysteroscopies.

In all procedures, hysteroscopy preceded D&C, and were performed under general anesthesia. The cervix was dilated for insertion of the hysteroscope. The medium of insufflations was normal saline. After identifying the cornua and tubal ostia, the endometrial cavity was thoroughly inspected. The hysteroscope was then removed and the cervix was dilated further with Hegar dilators. Subsequently, a blind fractional D&C was performed. We utilized a standard 3mm Olympus rigid telescope, with a 30° oblique lens and a 4.5mm diagnostic sheath for continuous flow hysteroscopy (Olympus Winter & Ibe GmbH, Hamburg, Germany). Our study protocols were approved by the UMMC Medical Ethics Committee (Reference Number: 872.13).

Data analysis was performed using SPSS version 16.0. Sensitivity and specificity were calculated with 95% confidence intervals using the Wilson score for binomial proportions. (International Business Machines Corporation, 2009) To complement sensitivity and specificity, we also calculated the positive and negative likelihood ratios (LR+ and LR–) and post-test probabilities for each hysteroscopy finding. LR+ is defined as sensitivity/(1–sensitivity); LR– is (1–sensitivity)/specificity. Pretest probablility is defined as (True positive+False negative)/Total sample; Positive post-test probability is True positive/(True positive+False positive); and Negative post-test probability is False negative/(False negative+True negative). (Grimes and Schulz, 2005)

Results
The patients’ mean age was 53.0 (SD=10.1) years. There were 162(39.3%) Malays, 122(29.6%) Chinese, 110(26.7%) Indians, and 18(4.4%) patients of other ethnicities. A total of 165 (40.0%) patients attained menopause. The patients’ parity ranged from 0 to 10 with a mean of 2.6; whereas 92(22.3%) were nulliparous. Almost all patients (97.1%) did not use hormone replacement therapy (HRT).
The indications for hysteroscopy were post-menopausal bleed (35.0%), menorrhagia (31.3%), irregular menses (9.5%), prolonged menses (8.3%), Tamoxifen use (3.9%) and others (12.1%).

Hysteroscopy and histopathology results are as shown in Table 1. In cases of atrophic endometrium on hysteroscopy, inadequate histopathology sampling was considered valid and concordant, where otherwise non diagnostic. (Bettocchi et al., 2001)

Hysteroscopic impression and histopathology were concordant in 366(88.8%) subjects. Table 2 shows the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each hysteroscopic finding. Hysteroscopy demonstrated a high sensitivity and specificity for focal lesions such as polyps and fibroids. However, the sensitivity for hyperplasia was moderate (64.4%). About a third of each endometrial hyperplasia subtype (simple, atypical and complex atypical hyperplasia) was missed, with half (7 cases) misdiagnosed as malignancy. This was consistent with a reduced PPV for malignancy.

The results for computed LR and post-test probabilities are as shown in Table 2. LR+ for all pathological findings were high, exceeding 10; whereas LR− were generally less than 0.1 except for endometrial hyperplasia. Positive hysteroscopy finding greatly increased the probability of disease for respective endometrial pathology, with positive post-test probabilities exceeding 80% but only moderate for malignancy (positive post-test probability=0.62). However, hysteroscopy was especially effective in ruling out malignancy, besides focal lesions such as polyps and myoma with negative post-test probabilities of less than 5%.

**Discussion**

The results of our study reinforces the opinion that hysteroscopy is a sensitive and specific tool in diagnosing benign and malignant endometrial pathology. However, we found a lower sensitivity (64.4%) of hysteroscopy in identifying hyperplasia which may be
explained by the surgeon’s tendency to err on the side of caution causing over-diagnosis of malignancy. Similar results have been reported by various studies exhibiting a low sensitivity for hyperplasia ranging between 40.4% and 70%; besides a low PPV. (de Wit et al., 2003; El-khayat et al., 2011; Garuti et al., 2001; Lasmar et al., 2006) This appears to be more pronounced in complex and atypical hyperplasia. (Libéris et al., 2010) A review by Clark et al. summarizes that hysteroscopy has only moderate accuracy for detecting endometrial hyperplasia. (Clark et al., 2002) There is a paucity of data on usage of LR and post-test probability among single studies on hysteroscopy but among systemic reviews, LR+ and LR− were shown to consistently exceed 5 and less than 0.4 respectively. As we have reported, hysteroscopy is excellent in ruling out malignancy as in negative findings, post-test probability falls to 0.0%; in comparison to corresponding values of 4% and 5% for polyps and myomas respectively. (Clark et al., 2002; van Dongen et al., 2007)

While we used D&C as the ‘gold standard’, multiple studies reported a low sensitivity (30.2-46%) and high false negative rate. (Bettocchi et al., 2001; Ceci et al., 2002; Yarandi et al., 2010) This comes in agreement with Epstein et al. that 58% of polyps, 50% to 60% of hyperplasias and 11% of carcinomas were missed. (Epstein et al., 2001) Despite so, recent studies refute these findings, maintaining D&C as the ‘gold standard’ in diagnosing malignant endometrial pathology. (Barut et al., 2011; Yarandi et al., 2010) A study suggests that endometrial sampling be omitted in clearly atrophic endometrium as less than 1% will turn out to be hyperplasia. (Lo and Yuen, 2000) However, we found that under similar circumstances hysteroscopy missed four premalignant lesions (atypia, hyperplasia and metaplasia) detected by D&C. We also found that inadequate histological sampling with visually atrophic endometrium (84 cases) was safe and valid, missing only one case of simple hyperplasia (hysterectomy specimen, data not shown). Despite high sensitivity of hysteroscopy in diagnosing myomas, PPV was reduced due to a high false negative rate of D&C in diagnosing benign structural lesions as suggested by a study. (Angioni et al., 2008) Among the 54 subjects excluded due to hysteroscopic impression of “fluffy endometrium”, there was an overrepresentation of endometrial hyperplasia (20.4%) diagnosed by D&C.
However, majority of cases (55.6%) were normal endometrium. Hence, all this emphasizes the need for endometrial sampling.

There are several limitations in our study. Being retrospective in nature, inevitably some data were missing. Secondly, the same surgeon performed both the hysteroscopy and D&C, thus improving the accuracy of D&C. Third, hysterectomy was performed in only 45 (10.9%) subjects and therefore, D&C results were taken as the standard diagnosis. The strength of this study is that we measured sensitivity and specificity of hysteroscopy for each pathological finding. We also incorporated the usage of 95% confidence intervals, likelihood ratios and post-test probabilities.

**Conclusion**
Hysteroscopy is accurate for focal and malignant endometrial pathology but only moderate for hyperplasia. Endometrial sampling is recommended for all cases especially when suspecting hyperplasia or malignancy.

**Conflict of Interest Statement**
The authors declare no conflicts of interest.

**References**


### Tables

**Table 1: Distribution of Hysteroscopic and Histopathology Findings**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hysteroscopy n(%)</th>
<th>Histopathology n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferative/Secretory</td>
<td>117 (28.4)</td>
<td>131 (31.8)</td>
</tr>
<tr>
<td>Inadequate Sampling</td>
<td>-</td>
<td>84 (20.4)</td>
</tr>
<tr>
<td>Atrophic Changes</td>
<td>107 (26.0)</td>
<td>19 (4.6)</td>
</tr>
<tr>
<td>Benign Polyp</td>
<td>96 (23.3)</td>
<td>71 (17.2)</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>18 (4.4)</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Disordered Proliferative</td>
<td>-</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>Hyperplasia: Overall</td>
<td>35 (8.5)</td>
<td>-</td>
</tr>
<tr>
<td>Simple</td>
<td>-</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Atypical</td>
<td>-</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Complex Atypical</td>
<td>-</td>
<td>8 (1.9)</td>
</tr>
<tr>
<td>Endometrial Carcinoma</td>
<td>29 (7.0)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>Others</td>
<td>10 (2.4)</td>
<td>33 (8.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>412 (100)</strong></td>
<td><strong>412 (100)</strong></td>
</tr>
</tbody>
</table>
Table 2: Sensitivity, Specificity and Likelihood Ratios of Hysteroscopy with D&C as Reference

<table>
<thead>
<tr>
<th>Normal</th>
<th>Atrophic</th>
<th>Polyp</th>
<th>Leioymoma</th>
<th>Hyperplasia</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>87.6 (80.3-92.5)</td>
<td>99.0 (94.5-99.8)</td>
<td>97.8 (92.3-99.4)</td>
<td>99.0 (100.0-100.0)</td>
<td>64.4 (49.8-76.8)</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.0 (95.7-99.1)</td>
<td>97.1 (94.6-98.5)</td>
<td>97.8 (95.6-98.9)</td>
<td>99.2 (97.8-99.7)</td>
<td>98.4 (96.5-99.3)</td>
</tr>
<tr>
<td>PPV</td>
<td>94.3 (88.1-97.4)</td>
<td>91.6 (84.8-95.5)</td>
<td>92.7 (85.7-96.4)</td>
<td>83.3 (60.8-94.1)</td>
<td>82.9 (67.3-91.9)</td>
</tr>
<tr>
<td>NPV</td>
<td>95.4 (92.5-97.3)</td>
<td>99.7 (98.2-99.9)</td>
<td>99.4 (97.7-99.8)</td>
<td>90.0 (100.0-100.0)</td>
<td>95.8 (93.2-97.4)</td>
</tr>
<tr>
<td>LR+</td>
<td>44</td>
<td>34</td>
<td>45</td>
<td>132</td>
<td>39</td>
</tr>
<tr>
<td>LR−</td>
<td>0.13</td>
<td>0.01</td>
<td>0.02</td>
<td>0.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Pre-test</td>
<td>0.27</td>
<td>0.24</td>
<td>0.22</td>
<td>0.04</td>
<td>0.11</td>
</tr>
<tr>
<td>Post-test (+)</td>
<td>0.94</td>
<td>0.91</td>
<td>0.93</td>
<td>0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Post-test (−)</td>
<td>0.05</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.04</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; Post test (+): Positive post test probability; Post test (−): Negative post test probability

*Numbers in brackets indicate 95% confidence intervals*
Highlights

- Hysteroscopy is a sensitive and specific tool for diagnosing endometrial pathology.
- High positive (>10) and low negative (<0.2) likelihood ratios were observed.
- Moderate sensitivity was observed for endometrial hyperplasia.
- Hysteroscopy is excellent in ruling out malignancy and focal structural lesions.
- Endometrial sampling should not be omitted even in visually normal endometrium.