The value of hysteroscopy and transvaginal ultrasonography in the diagnosis of endometrial hyperplasia: a systematic review and meta-analysis

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Background: The systematic evaluation of the diagnostic value of hysteroscopy and transvaginal ultrasonography for endometrial hyperplasia.

Methods: A systematic search was performed using China Knowledge Network Database, Wanfang Chinese Database, China Biomedical Literature Database, China Science and Technology Journal Database, PubMed, Medline, The Cochrane Library, and web of science from their dates of inception to December 31, 2017, hysteroscopy and transvaginal ultrasonography were used for the diagnosis of endometrial lesions in those studies. Two researchers screened the literature, extracted data, and evaluated the methodological quality of the included studies independently based on the inclusion criteria.

Results: A total of 1,354 cases were incorporate into analysis from 9 diagnostic studies meta-analysis showed that the diagnostic accuracy of hysteroscopy for endometrial hyperplasia lesions were: combined sensitivity =0.73 (95% CI: 0.68–0.77), combined specificity =0.92 (95% CI: 0.90–0.93), combined positive likelihood ratio =9.87 (95% CI: 4.08–23.84), combined negative likelihood ratio =0.34 (95% CI: 0.22–0.52), combined diagnostic odds ratio =31.64 (95% CI: 10.34–96.78), area under the summary receiver operating characteristic curve =0.8830. The combined sensitivity of transvaginal ultrasonography for those lesions were 0.69 (95% CI: 0.64–0.74), combined specificity was 0.78 (95% CI: 0.76–0.81), combined negative likelihood ratio was 3.40 (95% CI: 2.46–4.70), combined negative likelihood ratio was 0.41 (95% CI: 0.34–0.50), combined diagnostic odds ratio was 8.94 (95% CI: 5.80–13.79), and area under the summary receiver operating characteristic curve was 0.8180.

Conclusions: Compared with transvaginal ultrasonography, hysteroscopy have higher sensitivity, specificity, and area under the summary receiver operating characteristic curve for the diagnose of endometrial hyperplasia, hysteroscopy should be selected priority as the auxiliary diagnosis.

Keywords: Endometrial hyperplasia; transvaginal ultrasonography; hysteroscopy; systematic review; meta-analysis

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Introduction

Pathologic endometrial hyperplasia is an endometrial proliferative lesion with irregular gland size, increased glandular mass, and increased interstitial ratio of glands. It is a common gynecological disorder and is often characterized by abnormal uterine bleeding (1). According to the 2014 edition of the World Health Organization pathological diagnosis classification, endometrial hyperplasia was classified into non-atypical endometrial hyperplasia and endometrial atypical hyperplasia depending on whether it has cell atypia; endometrial atypical hyperplasia is considered to be the precancerous lesions of the type I endometrial cancer (2). Diagnosis of endometrial hyperplasia is of great value in preventing the progression int endometrial cancer (especially type I endometrial cancer). Auxiliary examination techniques of endometrial hyperplasia include transvaginal ultrasonography (3), hysteroscopic examination or hysteroscopy guide biopsy (4), saline infusion sonography (5,6), magnetic resonance imaging (MRI) (7,8), computed tomography (CT) (9), cervical (10) and endometrial cytology (11), and diagnostic curettage (12). Among these methods, transvaginal ultrasonography and hysteroscopic examination are the two auxiliary examination methods used most commonly in clinical practice. The final diagnosis of endometrial hyperplasia was based primarily on histological results. However, there is no overall value analysis of hysteroscopic examination and transvaginal ultrasonography in the diagnosis of endometrial hyperplasia. Therefore, the aim of this study is to evaluate the diagnostic value of hysteroscopic and transvaginal ultrasonography examination for endometrial hyperplasia systematically using the meta-analysis method, in order to provide recommend auxiliary diagnostic method for such pathologic lesions.

Methods

Information retrieval

A total of 8 databases were searched in detail from inception of the database to December 2017. The databases that were searched include China Knowledge Network Database, Wanfang Chinese Database, China Biomedical Literature Database, China Science and Technology Journal Database, PubMed, Medline, The Cochrane Library, and web of science. The retrieval combined the following topic terms, free search terms and key words: “Endometrial Hyperplasia/ Simple Endometrial Hyperplasia/Complex Endometrial Hyperplasia/Atypical Endometrial Hyperplasia/ Hysteroscopic Examination/Hysteroscopy/Uterine cavity Endoscopy/diagnostic hysteroscopy/Transvaginal Ultrasonography/Ultrasonic Imaging/Transvaginal Sonography/Transvaginal Color Doppler”.

Inclusion and exclusion standard

Inclusion standard

(I) The type of research was diagnostic research, Mandarin and English were the preferred languages; (II) the research target was patients with endometrial hyperplasia as diagnosed by gold standard to have endometrial cancer (pathological diagnosis) methods who formed the cases group. Those with other endometrial benign diseases, or healthy women were used as the control group; (III) the outcome index comprised of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, area under the summary receiver operating characteristic curve, and the Cochrane-Q index.

Exclusion standard

The following were excluded from the search: (I) Conference papers, reviews, lectures, abstracts, and other relevant published materials; (II) unavailable full texts papers; (III) literature with lack of significant information or with poor data integrity; (IV) self-control clinical trials.

Document quality evaluation

The quality of the literature was evaluated with QUADAS-2 quality evaluation standard (13,14). The QUADAS-2 tool is mainly composed of case selection, evaluation test, gold standard, test procedure, and time interval. It uses “yes”, “no”, or “unclear” to answer the relevant question. The answer is then used to determine the methodological quality of the included studies.

Data extraction

Two researchers screened the literature, extracted data, and evaluated the quality of the literature based on the inclusion and exclusion standard independently. They used self-made data extraction forms, which included the following information: basic information in the literature, patient characteristics, number of samples, hysteroscopic diagnosis, vaginal ultrasound diagnosis, pathologic diagnosis, the number of true positive cases, false positive cases, false
negative cases, and true negative cases.

**Statistical processing**

Data-analysis was performed using Review Manager 5.3, Stata 13.0, and Metadisc 1.4 software. according to the implementation guidelines for the evaluation of diagnostic test systems by Devillé et al. (15), we calculated the combined sensitivity, combined specificity, combined positive likelihood ratio, combined negative likelihood ratio, combined diagnostic odds ratio, and the corresponding 95% CI to obtain the diagnostic value of hysteroscopy and transvaginal ultrasonography for endometrial hyperplasia. We also plotted a summary receiver operating characteristic curve and calculated its area under the summary receiver operating characteristic curve and the Cochrane-Q index in our investigation. The test level for the meta-analysis was $\alpha=0.05$. Deeks funnel plots were used to analyze potential publication bias.

**Results**

**Information retrieval results**

A total of 529 related articles were detected at the beginning of this study, and after thorough reading and screening by layer, 9 studies were accepted for our investigation finally (16-24). The literature screening process and results was as shown in Figure 1.

**Basic characteristics and quality of selected literature**

The basic characteristics of the included studies was as shown in Table 1, and the results of the evaluation of
Table 1 Basic characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Research design</th>
<th>Age (year)</th>
<th>Total number of objects (person)</th>
<th>Endometrial hyperplasia</th>
<th>Non-endometrial hyperplasia</th>
<th>Method</th>
<th>TP (n)</th>
<th>FP (n)</th>
<th>FN (n)</th>
<th>TN (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bingol et al., 2011 (16)</td>
<td>Turkey</td>
<td>P</td>
<td>61.60±9.60</td>
<td>137</td>
<td>39</td>
<td>98</td>
<td>HM</td>
<td>37</td>
<td>1</td>
<td>2</td>
<td>97</td>
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<tr>
<td>Chen et al., 2015 (17)</td>
<td>China</td>
<td>R</td>
<td>38.88±10.28</td>
<td>208</td>
<td>56</td>
<td>152</td>
<td>HM</td>
<td>32</td>
<td>29</td>
<td>24</td>
<td>123</td>
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<tr>
<td>Li et al., 2015 (18)</td>
<td>China</td>
<td>R</td>
<td>45.50±5.50</td>
<td>192</td>
<td>60</td>
<td>132</td>
<td>HM</td>
<td>49</td>
<td>8</td>
<td>11</td>
<td>124</td>
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<tr>
<td>Mukhopadhyay et al., 2007 (19)</td>
<td>India</td>
<td>P</td>
<td>44–55</td>
<td>85</td>
<td>14</td>
<td>71</td>
<td>HM</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>68</td>
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<tr>
<td>Garg et al., 2016 (20)</td>
<td>India</td>
<td>P</td>
<td>Average 46.315</td>
<td>60</td>
<td>27</td>
<td>33</td>
<td>HM</td>
<td>17</td>
<td>18</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Xu et al., 2007 (22)</td>
<td>China</td>
<td>P</td>
<td>59.20±6.70</td>
<td>89</td>
<td>6</td>
<td>83</td>
<td>HM</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>Yang et al., 2016 (23)</td>
<td>China</td>
<td>R</td>
<td>45.31±6.27</td>
<td>252</td>
<td>56</td>
<td>196</td>
<td>HM</td>
<td>38</td>
<td>11</td>
<td>18</td>
<td>185</td>
</tr>
<tr>
<td>Yao et al., 2008 (24)</td>
<td>China</td>
<td>R</td>
<td>27–65, average 46.1</td>
<td>86</td>
<td>14</td>
<td>72</td>
<td>HM</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>69</td>
</tr>
</tbody>
</table>

Because the inclusion criteria for each study are not identical, the non-endometrial proliferative patients in the table include patients with endometrial cancer and/or other benign diseases of the endometrium and/or healthy women. P, prospective research; R, retrospective research; HM, hysteroscopy examination; TU, transvaginal ultrasonography.
literature quality was as shown in Figure 2. The 9 studies included a combined total of 1,354 cases, 350 were diagnosed with endometrial hyperplasia. Four of the studies (16,19,20,22) were prospective studies while five were retrospectively designed (17,18,21,23,24). All studies didn’t mention the specific recruitment methods. But there were still some risks on bias, applicability concerns for the index test and applicability concerns of patient selection: Regarding risk of bias for the patient selection, one study was labeled as having high bias (22). Regarding applicability concerns for the index test, one study did not prespecify the diagnostic threshold (24). Regarding applicability concerns for the patient selection, one study was labeled as having high bias (19).

**Systematic review results**

Results of the heterogeneity test showed no heterogeneity arising from threshold effects in the dates (Spearman correlation coefficient for hysteroscopic examination =-0.343, P=0.366; Spearman correlation coefficient for transvaginal ultrasonography examination =0.092, P=0.814). The summary receiver operating characteristic curve plan, which does not have a “shoulder arm” distribution, suggested that there is no heterogeneity caused by the threshold effect. In the diagnostic odds ratio forest map, the diagnostic odds ratio and the combined diagnostic odds ratio for each study were not distributed along the same line, indicating that heterogeneity was caused by non-threshold effects. The combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with the Cochrane-Q index for hysteroscopic examination was 0.73, 0.92, 9.87, 0.34, and 70.9 respectively (P<0.05), and their corresponding I² values was 76.0%, 90.8%, 92.9%, 81.2%, and 88.7% respectively. The combined sensitivity, specificity, positive
Figure 3  The summary receiver operating characteristic curve and Deeks funnel plot. (A) The summary receiver operating characteristic curve of hysteroscopic examination; (B) the summary receiver operating characteristic curve of transvaginal ultrasonography examination; (C) Deeks funnel plot for Publication bias of hysteroscopic examination; (D) Deeks funnel plot for publication bias of transvaginal ultrasonography.

likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with the Cochrane-Q index for transvaginal ultrasonography was 0.69, 0.78, 3.40, 0.41, and 161.11 (P<0.05) respectively, and their corresponding I² values were 5.3%, 87.0%, 75.1%, 28.9%, and 50.3% respectively.

Meta-analysis results were as shown in Figure 3 and Figure S1. The combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with hysteroscopic examination for the diagnosis of endometrial hyperplasia was 0.73 (95% CI: 0.68–0.77), 0.92 (95% CI: 0.90–0.93), 9.87 (95% CI: 4.08–23.84), 0.34 (95% CI: 0.22–0.52), and 31.64 (95% CI: 10.34–96.78) respectively. The combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio with transvaginal ultrasonography for the diagnosis of endometrial hyperplasia was 0.69 (95% CI: 0.64–0.74), 0.78 (95% CI: 0.76–0.81), 3.40 (95% CI: 2.46–4.70), 0.41 (95% CI: 0.34–0.50), and 8.94 (95% CI: 5.80–13.79) respectively. The area under the summary receiver operating characteristic curve for hysteroscopic examination and transvaginal ultrasonography was 0.8830 and 0.8180 respectively, and the corresponding Cochrane-Q index indices was 0.8135 and 0.7518 respectively.

Publication bias evaluation

Deeks funnel plot tests did not show publication bias for hysteroscopic examination and transvaginal ultrasonography (P>0.05, Figure 3).

Discussion

Endometrial cancer is one of the most common gynecologic malignancy in China (25). It is generally posited that endometrial atypical hyperplasia is the precancerous lesion of type I endometrial cancer. Endometrial hyperplasia has become one of the focuses of attention in the field of gynecology. Improving the diagnostic accuracy and identifying the pathological type is crucial to improve the prognosis of women with the subsequent disease.

Diagnostic curettage is widely used in the diagnosis of gynecological diseases, and was the main method used in the
diagnosis of endometrial atypical hyperplasia in the past (26). However, endometrial atypical hyperplasia may often be accompanied by local cancer, and diagnostic curettage may miss the diagnosis of endometrial cancer due to examination blindness typical of this method (27). Transvaginal ultrasonography has the advantages of being non-invasive, convenient, economical, easy to operate, reproducible, and painless. It can show irregular endometrial contours or abnormal endometrial thickness, and good repeatability characteristic in suggesting such endometrial lesions (3,28). A number of studies (29-31) proposed that women with post-menopausal vaginal bleeding and endometrial thickness ≥4–5 mm should be recommended to receive endometrial biopsy. Hysteroscopy is a minimally invasive technique that allows direct observation of the endometrium, particularly at the bilateral fallopian tube opening. Uterine cavity and endometrial morphology under hysteroscopic examination can improve diagnostic sensitivity and accuracy (32). Under hysteroscopy, the endometrium of patients with endometrial hyperplasia may show local or diffuse hyperplasia, and some may have single or multiple protrusions, which may be honeycomb or mesh. If it is grayish white or yellow, or a heterogeneous blood vessel with a large distribution, endometrial atypical hyperplasia or endometrial cancer should be highly suspected (33). In theory, hysteroscopic biopsy is superior to blind diagnostic curettage and can detect blind missed lesions; it has a high diagnostic accuracy for endometrial hyperplasia. Some studies have shown that the use of hysteroscopy for the diagnosis of endometrial lesions is more accurate than for the exclusion of endometrial lesions (34); its diagnostic value in endometrial lesions is receiving much more attention latterly. In Evaluating Postmenopausal Asymptomatic Women with thickened Endometrium, hysteroscopy allows an accurate diagnosis of benign endometrial pathology and suspected malignant endometrial pathology, avoids biopsy in case of atrophic endometrium (35).

This study included a diagnostic test comparing the diagnostic value of hysteroscopic examination and transvaginal ultrasonography for endometrial hyperplasia in the same population. According to the meta-analyses results, hysteroscopic examination has a higher sensitivity, specificity, and area under the summary receiver operating characteristic curve for the diagnosis of endometrial hyperplasia compared with transvaginal ultrasonography, and its diagnostic efficiency is higher. This study directly compares the combined values of the meta-analyses of the diagnostic indicators of the two examination methods. Hysteroscopy can be an extremely well tolerated and effective tool to diagnose uterine disorder. But Its complications can be severe and life-threatening, it is essential that the surgeon, with proper training and education, understands and is ready to manage the potential complications (36).

Nevertheless, there were notable limitations in this study. For instance: (I) the overall quality of the included studies was not high, and may have potentially affected the reliability of the conclusions; (II) in the inclusion and exclusion criteria of this study, other features that may have affected hysteroscopic examination and ultrasonography, such as menstrual status, type of biopsy, type of instrument (office hysteroscopy or resectoscopy) were not included, potentially causing a bias in the conclusion of the study; (III) moreover, this systematic review included Chinese and English literature only, yet didn’t rule out the possibility of language bias. Hence, with reference to the quality and quantity limitations of the included studies, further studies are necessary in the future to substantiate and validate these conclusions.

Conclusions

Hysteroscopy is better than transvaginal ultrasonography for the diagnose of endometrial hyperplasia, because of its higher sensitivity, specificity, and area under the summary receiver operating characteristic curve. More randomised controlled trials should be done in this area.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References


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Figure S1 Meta-analysis of hysteroscopic examination and transvaginal ultrasonography in the diagnosis of endometrial hyperplasia. (A) Combined sensitivity of hysteroscopic examination; (B) combined sensitivity of transvaginal ultrasonography; (C) combined specificity of hysteroscopic examination; (D) combined specificity of transvaginal ultrasonography; (E) combined positive likelihood ratio of hysteroscopic examination; (F) combined positive likelihood ratio of transvaginal ultrasonography; (G) combined negative likelihood ratio of hysteroscopic examination; (H) combined negative likelihood ratio of transvaginal ultrasonography; (I) combined diagnostic odds ratio of hysteroscopic examination; (J) combined diagnostic odds ratio of transvaginal ultrasonography.