Simultaneous Endometrial Aspiration and Sonohysterography for the Evaluation of Endometrial Pathology in Women Aged 50 Years and Older

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OBJECTIVE: To evaluate the performance of simultaneous endometrial aspiration at the time of sonohysterography for screening postmenopausal women at risk for endometrial cancer.

METHODS: A retrospective cohort study of women older than 50 years who underwent saline-infusion sonohysterography for the evaluation of their endometrium. On completion of imaging, the remaining intracavitary saline and endometrial tissue were aspirated through the saline-infusion sonohysterography catheter and submitted for pathologic evaluation. Based on the clinical, pathologic, and ultrasonographic results, the patients underwent surgical treatment with hysteroscopy, hysterectomy, or clinical observation. Follow-up results and outcomes were collected using electronic medical records. Sensitivity, specificity, and predictive values of saline-infusion sonohysterography, endometrial aspiration, and combined approaches for endometrial aspiration and sonohysterography were assessed.

RESULTS: Six hundred three patients underwent endometrial aspiration at the time of sonohysterography. Endometrial tissue was present in 567 (94.0%) and outcome data were available for 540 (89.5%). In 194 (35.9%) patients, final pathology was obtained by surgical intervention. The remaining 346 (64.1%) patients were monitored for at least 6 months. Thirty patients (5.6%) had cancer or endometrial hyperplasia. A sequential model, in which endometrial aspiration was done only for positive saline-infusion sonohysterography findings, yielded sensitivity of 86.7% (95% confidence interval [CI] 69–96%) and specificity of 100% (95% CI 99–100%) for detecting endometrial hyperplasia or cancer (area under the curve 0.93). Considering proliferative endometrium as abnormal endometrial aspiration reduced specificity to 88.3% (95% CI 85–91%, P < .01) without significant increase in sensitivity (100%, 95% CI 88–100%, P = .13).

CONCLUSION: The high sensitivity and specificity of the sequential endometrial aspiration at the time of sonohysterography make this approach a useful and reliable screening algorithm for detecting endometrial cancer or hyperplasia in postmenopausal women at risk. Endometrial aspiration at the time of sonohysterography should be considered as an initial one-stop endometrial evaluation in this population.

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LEVEL OF EVIDENCE: II

Endometrial cancer is the most common gynecologic malignancy in the United States and more than 90% of cases occur in women older than age 50 years. Abnormal uterine bleeding is the most common presenting symptom and therefore any woman presenting with postmenopausal bleeding should undergo evaluation to exclude endometrial hyperplasia or malignancy. The gold standard for the diagnosis of endometrial cancer or endometrial hyperplasia is complete histologic evaluation obtained either through curettage with hysteroscopy for complete evaluation...
of the uterine cavity or hysterectomy. Because most cases of postmenopausal bleeding are not associated with cancer, a screening procedure would help identify those who are at significant risk for cancer or hyperplasia. Compared with dilation and curettage, this procedure should be safer, more reliable, less expensive, and better tolerated by the patients.

Currently, the American College of Obstetricians and Gynecologists recommends two optional screening approaches for patients with postmenopausal bleeding: office endometrial biopsy or transvaginal ultrasonography for the measurement of endometrial thickness.\(^2,3\) In recent years, the addition of saline-infusion sonohysterography was incorporated into the workup for patients in whom the endometrial echo is thick or not adequately seen.\(^4\)

Since 2008, we began to include histologic evaluation of the saline aspirated from the uterine cavity at the end of saline-infusion sonohysterography. We present a large-scale study evaluating an approach that combines the currently two recommended methods into one procedure by adding endometrial aspiration to saline-infusion sonohysterography for screening women older than 50 years old who are at risk for endometrial cancer.

**MATERIALS AND METHODS**

This is a retrospective analysis of data collected on saline-infusion sonohysterography procedures performed between July 2008 and December 2013. Women aged 50 years and older, who had an evaluation of postmenopausal bleeding or thick endometrium or a suspected polyp on a prior scan, were included. Women with known cancer or hyperplasia were excluded. The institutional review board of Montefiore Medical Center approved the study (#11-04-138E).

Data were collected by two of the authors (M.R. and G.D.) from the different electronic medical records sources: ultrasound reporting system, hospital medical records for patient characteristics and pathology reports, and electronic patient folders for operative reports. Data were reviewed by three of the authors (O.R., P.D., and L.R.) at the conclusion of data collection. In case of inconsistency, electronic medical records and health care providers’ charts were reviewed by the lead author for validation. In all cases, management decisions were made by the individual health care providers, including the decision on primary workup by endometrial sampling, referral for transvaginal pelvic ultrasonography, referral for saline-infusion sonohysterography, or a combined approach. All saline-infusion sonohysterography procedures were performed in one of two ultrasound units by the primary investigator (O.R.). Saline-infusion sonohysterography was performed in the lithotomy position as described previously\(^5\) using a 2.3-mm diameter UNI-SEM catheter. After adequate exposure of the cervix with a speculum and cleaning with Betadine solution, the catheter was inserted through the cervical canal into the uterus. If the catheter could not be passed through the cervical canal secondary to cervical stenosis, the cervix was dilated using sequential thin cervical dilators. A transvaginal ultrasound probe was then inserted, and approximately 5–20 mL of sterile saline solution was injected slowly under direct ultrasonographic visualization. A three-dimensional volume acquisition as

![Image](https://example.com/fig1.png)

**Fig. 1.** Anteverted uterus with submucosal leiomyoma and endometrial thickening in a postmenopausal woman with vaginal bleeding. Although blind aspiration would probably sample the normal-appearing endometrium, ultrasonographic-guided aspiration (delineated with the arrow) of the focal lesion in the anterior wall might improve the ability to detect pathology in the focal lesion.

as well as two-dimensional sagittal and transverse images of the uterus were obtained using a Voluson 730 Expert or Voluson E8 Expert scanner with a three-dimensional 5- to 9-MHz transvaginal transducer. At the completion of the saline-infusion sonohysterography, before the removal of the catheter, the plunger of the syringe was retracted, creating negative pressure in the syringe, aspirating the remaining fluid as well as endometrial tissue under ultrasound guidance. When a focal lesion was identified, the catheter was either pushed or pulled so its edge was in direct contact with the lesion; the structure was then irrigated with saline and aspirated under ultrasonographic guidance (Fig. 1) (Videos 1 and 2, available online at http://links.lww.com/AOG/A597 and http://links.lww.com/AOG/A598, respectively). The catheter was then removed and the specimen was sent in a formalin container for histologic evaluation, as done routinely for an endometrial biopsy. Both ultrasonographic and histologic results were communicated to the health care providers who were responsible for further management of the patient.

We defined saline-infusion sonohysterography findings as negative if a smooth, thin, sharply contoured cavity and uniform-appearing endometrium were noted. Positive saline-infusion sonohysterography findings included polyps, focal lesions, and thickened endometrium. Thickened endometrium was defined as a double-layer endometrial echo of greater than 5 mm. We reported the presence of fibroids but did not categorize them as positive as a result of their low malignant potential, the fact that they are unlikely to be the source of bleeding in postmenopausal women, and because they were a frequent occurrence in our population.

Histologic endometrial aspiration findings were considered “normal” if read by the pathologist as atrophic, inactive, or secretory endometrium. Findings were considered “abnormal” if a simple or complex hyperplasia, endometrial cell atypia, or malignancy was identified. We found it difficult to categorize proliferative endometrium as either normal or abnormal. Although it may be common and physiologic in the endometrium of a 50-year-old perimenopausal woman, it is probably abnormal in the endometrium of a postmenopausal woman. In this study we analyzed the performance of simultaneous endometrial aspiration and sonohysterography twice, categorizing...
proliferative endometrium cases once as normal and once as abnormal. On final pathology, we categorized simple or complex hyperplasia, endometrial cell atypia, or malignancy as the cancer group.

Patient age and body mass index (BMI, calculated as weight (kg)/[height (m)]^2) were expressed as medians and ranges and ethnicity was expressed as frequency and percent. Saline-infusion sonohysterography findings, endometrial aspiration pathology, and endometrial biopsy pathology results were compared with either final surgical pathology or clinical follow-up data. The latter required one of the following occurring at least 6 months from the saline-infusion sonohysterography: no documentation of postmenopausal bleeding in a health care provider’s note, a repeated scan demonstrating endometrial lining of less than 5 mm, or a negative office endometrial biopsy result. We calculated sensitivity, specificity, positive predictive value, and negative predictive value of saline-infusion sonohysterography findings, endometrial aspiration pathology, and endometrial biopsy pathology. We calculated 95% confidence intervals (CIs) for sensitivity, specificity, positive predictive value, and negative predictive value for saline-infusion sonohysterography findings, endometrial aspiration pathology, and endometrial biopsy. To compare sensitivities and specificities between different methods, we used McNemar’s test. In addition, we ran a logistic regression model to determine the area under the curve (AUC) using receiver operating characteristic analysis to determine model fit.

To assess the screening performance of saline-infusion sonohysterography combined with endometrial aspiration, we used two approaches. First, we used sequential testing, which is a two-stage screening approach. For this analysis, we took all those who were considered to have a positive saline-infusion sonohysterography finding and then examined the sensitivity, specificity, positive predictive value, and negative predictive value of their endometrial aspiration results. A result was defined as “true-positive” only if the patient had positive saline-infusion sonohysterography and normal endometrial aspiration findings and had final pathology consistent with cancer or hyperplasia. A result was considered a “true-negative” if there was a normal endometrial aspiration finding and final pathology did not reveal cancer or hyperplasia or if, after 6 months or more of observation, the patient was clinically deemed as low risk for endometrial cancer. The sequential analysis was done twice: once including and once excluding patients with proliferative endometrium in the abnormal endometrial aspiration group. The advantage of this approach is a reduction of the number of false-positive results. To calculate the net sensitivity and net specificity based on sequential testing, we used the following equations:

Net Sequential Sensitivity
= Sensitivity SIS \times \text{Sensitivity EA},

Net Sequential Specificity = \text{Specificity SIS + Specificity EA} \times \text{Specificity SIS},

SIS, saline-infusion sonohysterography; EA, endometrial aspiration.

The second approach was to calculate the net sensitivity and the net specificity using these tests simultaneously and additively. A result was considered true-positive if it identified as positive on saline-infusion sonohysterography, endometrial aspiration, or both tests; that is, a positive result on either test would result in a diagnostic workup. A case was considered as true-negative if both saline-infusion sonohysterography and endometrial aspiration were negative and if final pathology did not reveal cancer or hyperplasia or if a patient was clinically asymptomatic and considered low risk for cancer after at least 6 months of follow-up. The net sensitivity and net specificity for this scenario were calculated by the following:

Net Simultaneous Sensitivity = \text{Sensitivity SIS + Sensitivity EA} \times \text{Sensitivity EA},

Net Simultaneous Specificity = \text{Specificity SIS \times Specificity EA},

SIS, saline-infusion sonohysterography; EA, endometrial aspiration.

SAS 9.3 was used for all statistical analyses and P<.05 was considered statistically significant.

RESULTS

Six hundred forty-four women were scheduled to undergo saline-infusion sonohysterography and it was successfully performed in 603 (93.6%) patients (Fig. 2). Forty-one (6.4%) cases were aborted secondary to cervical stenosis or the patient’s inability to tolerate the procedure. In all 603 patients in which saline-infusion sonohysterography was successfully performed, endometrial aspiration was sent to pathology. In 282 cases, an office endometrial biopsy, using a Pipelle device, was done within 4 months of the saline-infusion sonohysterography procedure by the health care providers.

The median patient age was 59.0 years (range 50–90 years) with 94 (15.6%) women 70 years or older and 23 (3.8%) 80 years or older (Table 1). The most common ethnicity was African American (49.3%). The median BMI was 31.9 (range 15–63.7). The most common
indication for saline-infusion sonohysterography was postmenopausal bleeding, present in 445 (73.8%) patients. There were no known cases of significant post-procedural complications.

Of 603 saline-infusion sonohysterography specimens sent for histologic evaluation, endometrial tissue was present in 567 (94.0%) (Fig. 2). Twenty-seven (4.8%) patients had no further documentation on management after undergoing endometrial aspiration at the time of sonohysterography. The remaining 540 women had documented outcomes and follow-up data for at least 6 months after the procedure. One hundred ninety-four (35.9%) patients had surgery and the tissue for final pathology was obtained through hysteroscopy, curettage, or hysterectomy. Median time between saline-infusion sonohysterography and surgery was 90 days (range 9–1,260 days). Thirty (5.6%) patients were diagnosed with either endometrial cancer or hyperplasia (Table 2). Eighteen patients had endometrial carcinoma, three had carcinosarcoma, and nine had endometrial hyperplasia (five with cytologic atypia, one with complex hyperplasia without atypia and three with simple hyperplasia without atypia). Their median age was 62.5 years (range 50.0–89.0 years) and their median BMI was 35.0 (range 24.8–56.0).

In 28, the diagnosis was made on final pathology

### Table 1. Demographic and Clinical Characteristics of Patients Who Underwent a Saline-Infusion Sonohysterography Procedure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59 (50–90)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.9 (15.0–63.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>256 (49.3)</td>
</tr>
<tr>
<td>White</td>
<td>64 (12.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>35 (6.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>155 (30.0)</td>
</tr>
<tr>
<td>Indications for SIS</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal bleeding</td>
<td>445 (73.8)</td>
</tr>
<tr>
<td>Thick endometrium</td>
<td>92 (15.3)</td>
</tr>
<tr>
<td>Suspected polyp</td>
<td>56 (9.3)</td>
</tr>
<tr>
<td>Abnormal Pap</td>
<td>10 (1.7)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SIS, saline-infusion sonohysterography. Data are median (range) or n (%).

### Table 2. Characteristics and Findings of 30 Patients Diagnosed With Cancer or Hyperplasia on Final Pathology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62 (50–89)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.0 (24.8–56.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>White</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Postmenopausal bleeding</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td>SIS findings</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>30 (100)</td>
</tr>
<tr>
<td>Thick endometrium</td>
<td>14 (46.7)</td>
</tr>
<tr>
<td>Focal lesion</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Endometrial aspiration path</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Atypical endometrium</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Proliferative</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Endometrial biopsy path (n=13)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Atypical endometrium</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Proliferative</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Polyp</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Inactive</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>No endometrium</td>
<td>1 (7.7)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SIS, saline-infusion sonohysterography. Data are median (range) or n (%).
and in two, the diagnosis was made on office biopsy, but both were included in the cancer group only after their slides were reevaluated and the diagnosis confirmed. One patient with simple hyperplasia transferred her care to another medical center and another was treated for endometrial cancer with chemotherapy secondary to multiple medical comorbidities.

Three hundred forty-six patients did not have surgery and underwent observation. Ninety-nine patients (28.6%) were monitored for more than 6 months but less than 1 year and 247 (71.4%) were monitored for more than 1 year.

Of the 36 patients who did not have tissue in their endometrial aspiration specimen, nine had surgery for a suspected endometrial polyp, and all had benign pathology. One of them had a hysterectomy 13 months after the hysteroscopy as a result of persistent postmenopausal bleeding. Hysterectomy pathology was consistent with a well-differentiated endometrial cancer. It is unclear to us if this finding was missed at time of hysteroscopy or was new. The remaining 27 patients were monitored for at least 6 months and none had clinical or ultrasonographic suspicion for endometrial cancer or hyperplasia.

One hundred fifty-eight patients had saline-infusion sonohysterography for indications other than postmenopausal bleeding, mostly for thick endometrium or suspected polyp on a prior scan. The median age was 63 years, and median BMI was 30.7. One hundred ten (82.1%) of the patients had a positive finding in saline-infusion sonohysterography, mostly a focal lesion (75.5%), and endometrial aspiration was successful in 139 (88%). Two patients were diagnosed with endometrial cancer in this group. One had a focal thickening on saline-infusion sonohysterography and complex hyperplasia without atypia on her endometrial aspiration. She underwent hysterectomy 2 months later and was found to have a well-differentiated endometrial cancer stage 1B. The second patient had a well-differentiated endometrial cancer not identified by endometrial aspiration (case 3 in Table 3). The saline-infusion sonohysterography showed a polyp and endometrial aspiration showed proliferative endometrium. Four months after the saline-infusion sonohysterography, the patient had office endometrial biopsy for new-onset postmenopausal bleeding, showing proliferative endometrium, similar to endometrial aspiration results. The diagnosis of cancer was made 10 months later, after a hysteroscopic polypectomy was performed for persistent postmenopausal bleeding. The patient was treated with progestins and 6 months later had a normal office endometrial biopsy.

Saline-infusion sonohysterography, endometrial aspiration, and office endometrial biopsy findings are described in Table 4 and test performance including sensitivity, specificity, positive predictive value, and negative predictive value of saline-infusion sonohysterography, endometrial aspiration, and office endometrial biopsy are described in Table 5.

Three hundred ninety-eight (73.7%) women had positive saline-infusion sonohysterography findings (Table 4). Of these, 126 (31.7%) had thickened endometrium and 372 (68.3%) had a focal lesion identified in the endometrial cavity. Of those with a focal lesion, 280 (75.3%) had findings consistent with a polyp and 92 (24.7%) had focal endometrial thickening. Ninety patients had a myoma with a submucosal component. In 45 patients, this was the only intracavitary finding, and those were considered negative saline-infusion sonohysterography findings. All patients with cancer had positive saline-infusion sonohysterography findings. Saline-infusion sonohysterography had the highest sensitivity (100%) and lowest specificity (27.8%) of the three screens (Table 5).

Table 3. Cases in Which Endometrial Aspiration and Final Pathology Did Not Correlate

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (y)</th>
<th>BMI (kg/m²)</th>
<th>Indication</th>
<th>Endometrial Aspiration Pathology</th>
<th>Final Pathology</th>
<th>Time From Endometrial Aspiration (mo)</th>
<th>Endometrial Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>47</td>
<td>Postmenopausal bleeding</td>
<td>Proliferative endometrium</td>
<td>Endometrial cancer, grade 1, in background of hyperplasia</td>
<td>4</td>
<td>Not done</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>39</td>
<td>Postmenopausal bleeding</td>
<td>Proliferative endometrium</td>
<td>Complex hyperplasia with foci of atypia</td>
<td>24</td>
<td>Not done</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>33</td>
<td>Thick endometrium</td>
<td>Proliferative endometrium</td>
<td>Endometrial cancer, grade 1, in background of hyperplasia</td>
<td>14</td>
<td>Proliferative endometrium</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>45</td>
<td>Postmenopausal bleeding</td>
<td>Proliferative endometrium</td>
<td>Endometrial cancer within a polyp</td>
<td>2</td>
<td>Proliferative endometrium</td>
</tr>
</tbody>
</table>

BMI, body mass index.
Twenty-six (4.8%) aspirations contained tissue suspicious for malignancy or hyperplasia. Twenty-two (4.1%) specimens contained endometrial polyp tissue. Of 65 (12%) patients who had proliferative endometrium, 47 (72.3%) had positive saline-infusion sonohysterography findings and 18 (27.7%) had negative saline-infusion sonohysterography findings. Twenty-eight (77.8%) women with no endometrial tissue had positive saline-infusion sonohysterography findings. Their average age was 65.7 years and average BMI was 30.82. Most (91.7%) had focal thickening and only three (8.3%) had homogenously thick endometrium. Endometrial aspiration had 86.7% sensitivity for detection of endometrial cancer or hyperplasia and specificity of 100%. The remaining four patients who had a final diagnosis of cancer or hyperplasia had endometrial aspiration results showing proliferative endometrium and all had a polypoid structure on saline-infusion sonohysterography (Table 3). These four patients underwent hysteroscopic-directed curettage or polypectomy in which the cancer and hyperplasia were detected. In two of these patients, the time interval between the saline-infusion sonohysterography and final pathology was 14 months (grade 1 endometrial carcinoma on final pathology) and 24 months (complex hyperplasia on final pathology).

Of 282 patients who had additional office endometrial biopsies, endometrial tissue was present in 263 (93.2%). Of these, 12 (4.8%) patients were subsequently diagnosed with cancer or hyperplasia. The office endometrial biopsy identified correctly only seven of these cases. Interestingly, four of the undiagnosed cases were reported as inactive endometrium. The office endometrial biopsy therefore had the lowest sensitivity of all screens for endometrial cancer or endometrial hyperplasia (58%).

All individuals who had positive saline-infusion sonohysterography and abnormal endometrial aspiration findings (excluding proliferative endometrium) were followed-up with a surgical procedure. None of the patients had abnormal endometrial aspiration findings if saline-infusion sonohysterography was found to be low-risk.

Sequential screening results are detailed in Table 5. Two scenarios were studied: one without considering proliferative endometrium as abnormal endometrial

### Table 4. Saline-Infusion Sonohysterography and Endometrial Aspiration Pathology Results

<table>
<thead>
<tr>
<th>Results</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIS</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>398 (73.7)</td>
</tr>
<tr>
<td>Thick endometrium (greater than 5 mm)</td>
<td>126 (31.7)</td>
</tr>
<tr>
<td>Focal lesion</td>
<td>372 (68.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>142 (26.3)</td>
</tr>
<tr>
<td>Leiomyoma with submucosal</td>
<td>45 (31.6)</td>
</tr>
<tr>
<td><strong>Endometrial aspiration pathology</strong></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>183 (33.9)</td>
</tr>
<tr>
<td>Atrophic</td>
<td>147 (27.2)</td>
</tr>
<tr>
<td>Benign</td>
<td>73 (13.5)</td>
</tr>
<tr>
<td>Polyp</td>
<td>22 (4.1)</td>
</tr>
<tr>
<td>Progestosterone effect</td>
<td>14 (2.6)</td>
</tr>
<tr>
<td>Estrogen effect</td>
<td>9 (1.65)</td>
</tr>
<tr>
<td>Endometritis</td>
<td>1 (0.19)</td>
</tr>
<tr>
<td>Proliferative endometrium</td>
<td>65 (11.9)</td>
</tr>
<tr>
<td>Atypical endometrium</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Cancer</td>
<td>16 (2.8)</td>
</tr>
</tbody>
</table>

SIS, saline-infusion sonohysterography.

### Table 5. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of the Different Screening Methods for Endometrial Hyperplasia or Cancer by Surgical Pathology and Clinical Follow-Up

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIS (n=540)</td>
<td>100 (88–100)</td>
<td>27.8 (24–32)</td>
<td>7.5 (5–11)</td>
<td>100 (97–100)</td>
</tr>
<tr>
<td>Endometrial aspiration pathology (n=540)</td>
<td>86.7 (69–96)</td>
<td>100 (99–100)</td>
<td>100 (87–100)</td>
<td>99.2 (98–100)</td>
</tr>
<tr>
<td>Endometrial biopsy (n=251)</td>
<td>50 (21–79)</td>
<td>99.6 (98–100)</td>
<td>85.7 (42–100)</td>
<td>97.5 (95–99)</td>
</tr>
<tr>
<td>Sequential endometrial aspiration at the time of saline infusion sonohysterography (n=398 [73.7%])</td>
<td>86.7 (69–96)</td>
<td>100 (99–100)</td>
<td>100 (87–100)</td>
<td>98.9 (97–100)</td>
</tr>
<tr>
<td>Excluding proliferative endometrium</td>
<td>100 (88–100)</td>
<td>88.3 (85–91)</td>
<td>41.1 (30–53)</td>
<td>100 (99–100)</td>
</tr>
<tr>
<td>Including proliferative endometrium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simultaneous endometrial aspiration and saline infusion sonohysterography (n=540 [100%])</td>
<td>100 (88–100)</td>
<td>27.8 (24–32)</td>
<td>7.5 (5–11)</td>
<td>100 (97–100)</td>
</tr>
<tr>
<td>Excluding proliferative endometrium</td>
<td>100 (88–100)</td>
<td>24.3 (21–28)</td>
<td>7.2 (5–11)</td>
<td>100 (97–100)</td>
</tr>
<tr>
<td>Including proliferative endometrium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; SIS, saline-infusion sonohysterography.
aspiration and the other including proliferative endome-
trium in the abnormal endometrial aspiration group. 
Three hundred ninety-eight (73.7%) women had posi-
tive saline-infusion sonohysterography findings and 
were assessed based on their endometrial aspiration 
findings. On doing a sequential screening, 26 (4.8%) 
of the women would be considered screen-positive 
when proliferative endometrium cases were considered 
as normal endometrial aspiration results. The sensitivity 
of this approach was therefore 86.7% (95% CI 69–96%), 
with specificity of 100% (95% CI 99–100%; AUC 0.93). 
When proliferative endometrium cases were considered 
as abnormal endometrial aspiration results, 73 (13.5%) 
of the women would be considered screen-positive and 
would be recommended for further surgery. The 
sequential approach in this scenario would identify all 
cases of cancer or hyperplasia (sensitivity 100% [95% 
CI 88–100%]), but specificity would decrease to 88.3% 
(95% CI 85–91%; AUC 0.94). Considering proliferative 
endometrium cases as abnormal provides a significant 
decrease in specificity (P<.01) but no significant change 
to sensitivity (P=.13).

Simultaneous additive testing results are detailed 
in Table 5. Again, two scenarios were studied: one 
without considering proliferative endometrium as an 
abnormal endometrial aspiration and the other 
including proliferative endometrium in the abnormal 
endometrial aspiration group. Considering screen-
positive results if either of the steps is positive, 398 
(73.7%) would be considered screen-positive and 
would be recommended for further surgical manage-
ment. In this scenario, sensitivity would be 100% 
(95% CI 88–100%) but specificity would only be 
27.8% (95% CI 24–32%; AUC 0.64). If proliferative 
endometrium is considered an abnormal finding, 
specificity will be further decreased to 24.3% (95% 
CI 21–28%; AUC 0.50). Comparing sequential 
screening results with simultaneous screening results, 
we find no difference in sensitivity (P=.37) but signif-
icantly higher specificity with the sequential screening 
method (P<.01).

A total of 139 (71.6%) patients had confirmed 
polypoid tissue on pathology. Only in 17 (12.2%) 
patients was an ultrasonographic diagnosis of a polyp 
the sole indication for proceeding with hysteroscopy 
or hysterectomy. In three additional patients, the 
health care provider who performed the procedure 
reported on visual polyps, but this was not confirmed 
by histologic evaluation. In three patients, complex 
hyperplasia was found within the polyp. Of 139 
polyps diagnosed on hysteroscopy or hysterectomy, 
endometrial aspiration identified polypoid tissue in 
only 14 (10.1%) patients. Similarly, office endometrial 
biopsy identified polypoid tissue in only seven (5.0%) 
of these patients.

DISCUSSION

In this study, we present a combined and simultaneous 
ultrasonographic and histologic approach to screen 
women older than 50 year old with clinical or 
ultrasonographic suspicion for endometrial cancer. 
We show that this simultaneous endometrial aspiration 
at the time of saline-infusion sonohysterography is 
feasible, efficient, and, when used sequentially, provides 
excellent sensitivity and specificity for the detection of 
hyperplasia or malignancy. In particular, the high 
sensitivity of saline-infusion sonohysterography is 
complemented by the high specificity of endometrial 
aspiration. The approach allows evaluation of post-
menopausal bleeding or abnormal-appearing endome-
trium ultrasonographically and pathologically in one 
procedure obviating the need for multiple office visits.

We analyzed the performance of endometrial 
aspiration at the time of sonohysterography using both 
sequential and simultaneous, or additive, algorithms. 
The simultaneous, or additive, approach did not add 
any benefit to performing saline-infusion sonohyster-
ography alone and resulted in very low specificity with 
more than 70% of the patients recommended to 
undergo further testing. The sequential approach in 
which endometrial aspiration is performed only if 
saline-infusion sonohysterography findings are posi-
tive and further surgery is recommended only if 
endometrial aspiration findings are abnormal 
yielded much higher specificity (P<.01).

We further examined two options for the sequen-
tial algorithm with categorizing proliferative endome-
trium in endometrial aspiration as either normal or 
abnormal. When proliferative endometrium was cat-
egorized as a normal endometrial aspiration finding, 
only 4.5% of the patients would have been considered 
screen-positive and referred for surgery, but 13.3% of 
patients with hyperplasia or malignancy would have 
been missed. In two of the four cases that would have 
been missed with this algorithm, the final diagnosis 
was made at 14 and 24 months after saline-infusion 
sonohysterography. It is possible, therefore, that the 
abnormal pathology was not actually present at the 
time of the endometrial aspiration and evolved over 
the interval period. When proliferative endometrium 
was categorized as an abnormal endometrial aspira-
tion result in the setting of a positive saline-infusion 
sonohysterography finding, sensitivity was 100% but 
pecificity was decreased to 88%, with approximately 
13% of patients recommended for further surgery.
Although the latter approach was not our standard practice during the study period, it is worthy of consideration.

Sampling of the endometrium during saline-infusion sonohysterography has been previously performed, but these studies reported mostly on premenopausal women and showed variable results.\textsuperscript{7–10} Leone\textsuperscript{10} compared directed biopsy using a 4.7-mm catheter with biopsies done during hysteroscopy and found this method as reliable and efficient. Metzger used a similar technique, however, with a thinner catheter of 3.1 mm and described opposite results—ultrasonographically guided endometrial biopsy had no effect on endometrial assessment by saline-infusion sonohysterography. Wei et al\textsuperscript{9} described saline-infusion sonohysterography directed extraction biopsy using an Explora curette of 3 mm in diameter, but in 12 of 13 patients (92%), only blood clots were obtained.

Moschos et al\textsuperscript{11} performed saline-infusion sonohysterography followed by the removal of the saline-infusion sonohysterography catheter and introduction of an endometrial sampling curette for ultrasonographically directed biopsy. They found that saline-infusion sonohysterography provided the diagnosis in 89% of women with abnormal uterine bleeding and performed better than endometrial biopsy, which provided the diagnosis in only 52% of the patients. Our study is different from the previously mentioned study, because we used the saline-infusion sonohysterography catheter for the ultrasonographic-directed biopsy without removing it. Furthermore, although the sensitivity of the office endometrial biopsy in this study is consistent with the sensitivity of the office endometrial biopsy reported in our study, the sensitivity of the directed endometrial aspiration was significantly higher.

The performance of office endometrial biopsy reported in the literature is also inconsistent with a wide range of sensitivity and specificity. Stovall et al performed endometrial sampling on 40 patients with known endometrial cancer before planned hysterectomy. They identified endometrial cancer in 39 of 40 patients, yielding a sensitivity of 97.5%.\textsuperscript{12} Huang et al\textsuperscript{13} confirmed that endometrial Pipelle biopsy was efficacious in detecting high-grade endometrial cancer. In contrast, a study by Ferry et al showed completely different results. In fact, in 12 of 37 patients with malignancy (33%), the cancer was missed.\textsuperscript{14} Similarly, Svirsky et al\textsuperscript{15} reported a poor performance of office endometrial biopsy, especially in the diagnosis of focal lesions. In a recent study by Demirkiran et al, Pipelle biopsy and dilation and curettage showed almost equal success rates in the diagnosis of endometrial pathology. The concordance rate was 67% between Pipelle and hysterectomy and 70% between dilation and curettage and hysterectomy. However, neither Pipelle nor dilation and curettage were found to be adequate methods for the diagnosis of focal endometrial lesions.\textsuperscript{16} In the current study, endometrial aspiration was more successful in obtaining endometrial tissue for analysis as well as detecting more cases of cancer compared with office endometrial biopsy.

Although the American College of Obstetricians and Gynecologists recommends that women with postmenopausal bleeding be assessed initially with either office endometrial biopsy or transvaginal ultrasonography,\textsuperscript{2} the management of postmenopausal bleeding by ultrasonography alone and without obtaining an endometrial sample is controversial. Goldstein reviewed five studies of women with postmenopausal bleeding. When the endometrial echo was less than 4 mm, he found only three cases of undetected cancers among 2,752 patients. That resulted in a risk of one in 917 for endometrial cancer in a patient with postmenopausal bleeding and a thin endometrium.\textsuperscript{3} Wang et al\textsuperscript{17} reported that a thin or indistinct endometrial stripe, especially when associated with other ultrasound abnormalities, did not reliably exclude type 2 endometrial cancer. Moreover, in a recent meta-analysis, Timmermans et al questioned the accuracy of transvaginal ultrasonography as a screening tool and advised a cutoff level of 3 mm for exclusion of endometrial carcinoma in women with postmenopausal bleeding. Using this cutoff will yield a sensitivity of 97% and specificity of 34%,\textsuperscript{18} similar to our findings with the use of saline-infusion sonohysterography alone. Using nonspecific methods will result in high numbers of invasive procedures, most of which prove unnecessary.

Saline-infusion sonohysterography is an excellent tool for detection of polypoid structures. Both endometrial aspiration and office endometrial biopsy, however, showed poor performance in identifying polypoid tissue, even through ultrasonographic-directed aspiration. This may be the result of the small catheter caliber, which is sufficient for superficial endometrial sampling but inadequate for obtaining larger tissue specimens.

There are several limitations to this study. One limitation is that this study is retrospective and is influenced by different management styles used by different health care providers. Nevertheless, this is a large data set that provides excellent follow-up data including a large number of final pathology results for high-risk screens. A second limitation is the lack of final pathology in all cases. It is clear,
however, that most cases of postmenopausal bleeding have a benign etiology. Therefore, many women with postmenopausal bleeding will require observation and not surgical intervention. Because it would not be reasonable to dismiss this large population, we considered patients with normal endometrial aspiration results who were clinically and ultrasonographically deemed low risk for cancer after 6 months of observation as comparable to patients who received a benign result on final pathology. Furthermore, even in a prospective study, it would not be medically justified to perform a surgery on these patients just to obtain final pathology. Finally, we included all women older than 50 years of age in the cohort, likely incorporating a few women who were perimenopausal. We felt that in a retrospective study, age would be a more definite criterion than a postmenopausal status. In fact, nine of the 30 of the women who had endometrial hyperplasia or cancer were younger than 60 years, stressing the importance of including this younger age group.

In conclusion, we present a large clinical study on combined and simultaneous saline-infusion sonohysterography and endometrial aspiration for women older than 50 years old with clinical or ultrasonographic suspicion for endometrial hyperplasia or cancer. Our findings suggest that a sequential endometrial aspiration at the time of a sonohysterography approach provides both high sensitivity and specificity for endometrial hyperplasia and cancer. Although promising as a screening paradigm, this approach warrants evaluation in a prospective clinical trial.

REFERENCES