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A New Diagnostic Test for Endometrial Cancer?:

Cytology Analysis of Sonohysterography Distention Media

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Abstract

Objective—During saline-infused sonohysterography (SIS), the distension fluid is typically discarded. If cytology analysis could identify those patients with endometrial cancer, many women would be spared from further procedures.

Methods—Thirty consecutive patients with clinical stage I or II endometrial adenocarcinoma were prospectively recruited preoperatively. Saline-infused sonohysterography was performed by instilling 5 mL of saline, withdrawing and sending for analysis. Saline was reinfused until complete SIS images were obtained and sent separately for cytology.

Results—Of the 30 women enrolled, SIS was technically successful in 29. Demographics included mean age (60.5 ± 6.99 years), body mass index (35.55 ± 8.18 kg/m²), endometrioid histology (76%), and grade (grade 1, 67%). Prestudy diagnostic method included biopsy (70%), dilatation and curettage (17%), and hysteroscopy (10%). Adequate cytology specimens were obtained in 66% of the 5mL flushes and 72% of the complete SIS collections. Of adequate specimens, the sensitivities to detect endometrial cancer for the 5-mL, complete, and combined fluid samples were 26% (95% confidence interval, 9%–51%), 36% (17%–59%), and 42% (22%–

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63%). Sensitivity based on the whole study sample (N = 30) was 33% (17%–53%). Statistical significance was not found in the association between a positive test and age, body mass index, grade, diagnostic method, or volume instilled or aspirated.

Conclusions—Most patients with early endometrial cancer can undergo SIS procedures with adequate cytology specimens obtained from distention media. However, the sensitivity is low, and refinements are necessary before utilizing as a diagnostic test. In cases with positive results, the patient may be able to avoid other costly and painful procedures.

Keywords

Saline-infused sonohysterography; Endometrial cancer; Cytopathology

Investigation of endometrial pathology is indicated in women with heavy or interval bleeding during the reproductive years, postmenopausal bleeding, and/or identification of thickened endometrium according to age. The management algorithm for such patients includes a combination of 1 or more of the following (depending on clinical suspicion): pipelle curettage, ultrasonography, saline-infused sonohysterography (SIS), dilatation and curettage (D&C), and hysteroscopy (with guided biopsy).

Although pipelle curettage is quick, inexpensive, and less invasive, a smaller portion of the total endometrial cavity is sampled compared with hysteroscopic-guided biopsy and D&C. Therefore, the diagnostic capacity is lower. Unfortunately, many women still require additional, often invasive, procedures to further evaluate abnormal bleeding, because of a significant number of missed lesions with pipelle sampling.^{1,2}

Saline-infused sonohysterography has an important role in evaluating the endometrium in women with perimenopausal/postmenopausal bleeding or space-occupying lesions in endometrial cavity. This procedure is relatively less complicated than hysteroscopy and has a reported sensitivity of 96%, specificity of 97% to 100%, positive predictive value of 96%, and negative predictive value of 97% in the diagnosis of endometrial lesions^{3,4} compared with hysteroscopy.

The idea of cytologic examination in endometrial washings goes back to 1972. Abate et al⁵ suggested a technique called “jet washing,” and Henderson et al⁶ suggested that endometrial samples obtained with the intrauterine jet washer provide information about the endometrium, which is comparable to that obtained by conventional curettage. Several authors evaluated this technique^{7–10} and concluded that the method was simple and might be of special value in postmenopausal patients. Moreover, tubal adenocarcinomas that had not been detected by curettage were suggested to be detected by intrauterine washing cytology.¹¹

A small number of studies have looked at cytology analysis of the distension media at the time of hysteroscopy as a predictor of endometrial pathology.^{12–16} Although the results are somewhat conflicting, Gerbaldo et al¹⁷ found endometrial cytology to be adequate in 94% of 243 patients. All cases of atypical cells on cytology represented either atypical complex hyperplasia or endometrial cancer at final histologic diagnosis. Actual cases of cancer were rare in these studies, and therefore sensitivity could not be precisely determined.

At the time of SIS, the distension fluid is typically aspirated to reduce postprocedure cramping and then discarded. However, if cytology analysis could identify those patients with endometrial cancer, many women would be spared from further invasive and uncomfortable procedures. In this study, we aimed to evaluate SIS distension fluid for

cytologic examination and assess the sensitivity of the SIS as a diagnostic test utilizing patients with a known diagnosis of endometrial cancer.

MATERIALS AND METHODS

This study was a prospective observational cohort conducted under a University of Wisconsin–Madison Health Sciences Institutional Review Board–approved protocol (H-2006-0333 approved on January 25, 2007) and was supported by the ACOG/Kenneth Gottesfeld–Charles Hohler Memorial Foundation Research Award in Ultrasound. Informed consent was obtained from all patients before their involvement in the trial, and the study was compliant with the Health Insurance Portability and Accountability Act of 1996. The study was registered in www.clinicaltrials.gov with the identity number NCT00462969 before enrollment.

Patient Selection

Thirty consecutive patients with clinical stage I (%) or stage II (%) endometrial adenocarcinoma undergoing primary surgical management at the University of Wisconsin Hospitals and Clinics were recruited at their preoperative visit between March 2007 and August 2010.

Inclusion criteria included endometrial adenocarcinoma of any grade, any preoperative diagnostic method, Gynecologic Oncology Group performance status of 0 to 2. Exclusion criteria included evidence of distant metastasis, younger than 18 years, previous hysterectomy, current pregnancy, active pelvic inflammatory disease, and stenotic cervical os.

SIS Technique

All SIS procedures were performed by 1 of 4 physicians experienced in this technique. A preliminary transvaginal ultrasound was performed in all patients to determine the basic anatomy, uterine position, approximate endometrial thickness, and possible tumor location. Subsequently, with the patients in the standard lithotomy position, a speculum examination was performed. The cervix was identified, and the speculum was utilized to optimally orient the cervix. The cervix was cleansed with iodine. A standard 5F SIS balloon-bearing catheter (Marshall Medical HSG Catheter; Marshall Medical Systems, Lombard, IL) was used. Before placement, it was flushed with sterile saline, and the air bubbles were removed from the catheter balloon. Subsequently, the cervix was cannulated with the catheter with the goal to place the catheter into the lower uterine segment. After the balloon was inflated with sterile saline, the speculum was removed, and the sterile, covered transvaginal ultrasound transducer was inserted (LOGIQ E9; GE Healthcare, Waukesha, WI). During continuous transvaginal imaging, an initial injection of 5 mL of sterile saline was performed and immediately aspirated. The aspirated fluid was sent to cytology as the “5 mL” sample. A full sonohysterography examination with sterile saline as the distention media was then performed with gray-scale, color Doppler, 3-dimensional, and cine images. At the conclusion of the study, any residual fluid was aspirated and sent to cytology as the “adequate SIS” sample. The volume of the samples was documented along with the volume required to complete the SIS. All images were saved to the PACS (Horizon Medical Imaging; McKesson, San Francisco, CA), and tumor size, location, and sonographic characteristics were documented.

Originally, we performed SIS procedures only in the outpatient setting. However, because of lower than expected accrual, we amended the protocol, and patients 22 to 30 were given the

option of having the procedure under general anesthesia in the operation room (just before their hysterectomy). As a result, 5 of these final 8 women chose this option.

True-Negative Samples

In order to increase the validity of the cytopathologist's diagnosis of cancer, "true-negative" samples were obtained and randomly interspersed among the study samples before the blinded readings occurred. A subset of consecutive patients undergoing SIS for clinical purposes in a reproductive endocrinology clinic was consented to have the fluid withdrawn and sent to pathology as blinding specimens as part of the institution review board-approved study. The identical procedure that is described above was used for the SIS and to obtain samples. These slides were evaluated by the first cytopathologist and confirmed as normal endometrium. These 10 negative slides were interspersed using random-number tables and numbered in an identical manner to the cancer specimens to not allow the second cytopathologist to determine the origin of the slides.

Cytologic Examination

The specimens were sent fresh to the cytology laboratory, prepared, and run on a ThinPrep 3000 processor, alcohol-fixed, Papanicolaou-stained, and cover slipped, all according to standard body fluid protocol. The slides were labeled with a study case number, batched, and examined by 1 cytopathologist (J.L.H.). Slides were screened for any cells or groups of cells with cytologic features of malignancy, including 3-dimensional cell clustering, nuclear enlargement, increased nuclear-to-cytoplasmic ratio, coarsening of chromatin, prominent nucleoli, and nuclear irregularity. Samples containing cells with some of these features but deemed not enough for a definitive malignant diagnosis were designated as atypical.

Statistical Analysis

Sensitivity was estimated as the proportion of cancer-positive specimens out of samples that were evaluable for the cytologic results. The same calculation was also performed based on the whole study samples, assuming that unevaluable samples would be cancer-negative. In an exploratory analysis only, univariate logistic regression was conducted with adequate samples for the cytologic test to examine the association between test positivity and relevant variables for the cytologic test. A sample size of 30 patients was designed to have an 87% of a lower-bound confidence interval (one sided 95% confidence interval [CI]) of sensitivity of 97%.

RESULTS

Thirty women with endometrial cancer were enrolled (mean age, 60.5 ± 6.99 years; mean body mass index [BMI], 35.55 ± 8.18 kg/m²), with SIS technically successful in 29 patients. In 1 patient, SIS failed because of inability to adequately fill the canal with distension fluid. Representative ultrasonographic appearances are presented in Figures 1A–C with positive cytologic examinations shown in Supplemental Figures 1A and B (available at <http://links.lww.com/IGC/A173>).

Prestudy diagnostic method included biopsy (70%), D&C (17%), and hysteroscopy (10%). Prestudy biopsy histology was endometrioid adenocarcinoma in 23 (76.6%), papillary serous adenocarcinoma in 3 (10%), adenosquamous type in 1 (3%), and adenocarcinoma not otherwise specified in 3 women (10%). Twenty subjects (66%) had grade 1 disease, 5 women had grade 2 disease, and only 4 women (13.3%) had grade 3 disease (Table 1).

Of samples evaluable for the cytologic examination, 5 (24%; 95% CI, 8%–47%) of 21 specimens were deemed cancer-positive in 5-mL initial flush group, 8 (30%; 95% CI, 14%–

50%) of 27 were cancer-positive in adequate SIS group, and 10 (37%; 95% CI, 19%–58%) of 27 were positive in total in the 5-mL initial flush group, and the adequate SIS sample group combined. Sensitivity based on the whole study samples (N = 30) was 33% (95% CI, 17%–53%), assuming that unevaluable samples would be cancer-negative, which is a more conservative approach for sensitivity.

Adequate cytology specimens were obtained in 66% of the 5-mL flushes and 72% of the complete SIS collections. Of adequate specimens, the sensitivities of the test to detect endometrial cancer for the 5-mL, complete, and combined fluid samples were 26%, 36%, and 42%, respectively (Table 2). There were no false-positive cases in the “true-negative” group.

In univariate logistic regression, statistical significance was not found in any variables in association with test positivity from either or both of the 2 methods (Table 3).

DISCUSSION

Our findings reveal that the sensitivities of SIS distention media to detect endometrial cancer for the 5-mL, adequate SIS, and combined fluid samples were the relatively low values of 26% (95% CI, 9%–51%), 36% (95% CI, 17%–59%), and 42% (95% CI, 22%–63%) in this population of patients with known stage I and II endometrial cancer. Sensitivity based on the whole study samples (N = 30) was 33% (95% CI, 17%–53%). However, our results and previous studies¹⁵ suggest that there may be a low likelihood of a false-positive test, such that it may provide some usefulness in identifying at-risk patients. Statistical significance was not found in the association between test positivity and age, BMI, grade, diagnostic method, and volume instilled or aspirated.

Pacifico et al¹⁸ performed 138 consecutive jet washings and reported that, in the 127 adequate specimens obtained (92%), all 16 endometrial carcinomas were diagnosed cytologically. However, Lewis and Chapman⁷ reported that the sensitivity of uterine washing in diagnosis of endometrial cancer was 15%, which is quite lower compared with the study of Pacifico et al.¹⁸ In the study of Lewis and Chapman,⁷ there were neither false-positive nor false-negative results reported.

There is debate as to the best method of endometrial cancer screening and diagnosis. Dilatation and curettage and hysteroscopy (with guided biopsy) are still considered by many as the criterion standard to diagnose endometrial pathology. However, the techniques involved in SIS are relatively simple—involving only a small catheter, physiological saline solution, and syringes. The success rate of SIS in postmenopausal women was as high as 86.5% and even higher in premenopausal women (95%).¹⁹ The only major contraindications of SIS are preexisting pelvic inflammatory disease and cervical stenosis.

Acquiring an adequate amount of cells is essential not only for sampling the widest area of endometrium, but also for optimal cytologic evaluation. Of course, it is not possible to know how large an area is sampled by SIS. In our study, we used standard 5F sonohysterography balloon-bearing catheters. Using a larger catheter might acquire a superior sample or larger returning fluid volumes. Since it is hypothesized that loosely adhered or shed cells are more easily sampled, the histologic type and tumor grade might also make a difference. It has been suggested that high-grade lesions shed more readily. However, even benign lesions such as hyperplasia or polyps were reported to be detected by intrauterine washings in prior reports.¹³ In our study, biopsy histology was endometrioid adenocarcinoma in 23 women (76.6%), and the differentiation level was grade 1 in 20 women (66%). The numbers of non-endometrioid cancer and high-grade cases were too small to draw conclusions on the effect of histologic type and grade on the success of the test.

A potential risk of SIS other than dissemination of preexisting infection could be the dissemination of the cancer cells via the fallopian tubes to peritoneal cavity. This potential risk was discussed by the prospective studies of Berry et al²⁰ and Bese et al.²¹ Berry et al²⁰ showed that 12 of 16 women with endometrial cancer had transtubal spill during SIS; however, only 1 patient had adenocarcinoma cells on cytologic analysis, which were later detected to be nonviable. Bese et al²¹ detected that 24 of 44 patients had transtubal spill during SIS, and 6 of these 24 women had adenocarcinoma cells on cytologic examination. The viability of these adenocarcinoma cells was not investigated. Peritoneal positivity alone is not considered to be a parameter for staging and is no longer staged as IIIa in the 2009 Federation of International of Gynecologists and Obstetricians classification. However, it is still reported in the pathology results separately and has debated significance on prognosis. In our study, we did not use jet washing by itself (with the extra pressure), without SIS because it provides little benefit compared with the potential risks. Questions remain as to whether endometrial cancer cells maintain viability and proliferate once they are displaced into the peritoneal cavity. Arikan et al²² performed in vitro hysteroscopy in 24 uteri with endometrial cancer after the specimens were removed surgically. For evaluation of viability of the disseminated cells, fluid samples were first analyzed with a trypan blue exclusion assay (mean viability, 90%) then cultured, incubated, and evaluated for adherence. Among the samples, 17 (71%) contained tumor cells, of which 42% demonstrated functional viability.

In a prospective study, Hirai et al²³ investigated the malignant potential of positive peritoneal washings in 50 cases of endometrial cancer. They obtained peritoneal washings by a tube on the 7th and 14th days postoperatively. Persistence of positive peritoneal washings was observed in 1 (2.9%) of 34 patients with stage IIIA cytologic and 5 (10%) of 50 of all cases. They suggested that endometrial cancer cells found in the peritoneal cavity disappeared within a short time and seemed to have a low malignant potential in patients with limited disease in comparison to patients with adnexal metastasis.

Berry et al²⁰ were the first to evaluate viability of endometrial cancer cells in an in vivo study of SIS. Disseminated endometrial cancer cells were observed only in 1 (6%) of 16 patients, and none of the cells demonstrated viability. However, 1 patient is not an adequate sample on which to base definitive conclusions.

The acceptability of endometrial aspiration cytology as a substitute for tissue pathology to diagnose endometrial cancer and initiation of treatment without first obtaining biopsy or D&C could be questioned. However, patients with many different malignancies are treated after only needle aspiration and cytology diagnosis. Regardless of the grade and cell type, endometrial cancer is surgically staged, and the standard treatment for endometrial cancer is surgery. The final surgical specimen is what truly determines the prognosis and treatment options. The answer to this question will require further study. If the positive predictive value of endometrial aspiration cytology could be proven to be high enough in a larger trial, then it may be possible to recommend it as a feasible and safe procedure to proceed to an invasive treatment.

Although the overall sensitivity of this diagnostic test is low, that does not rule out potential future clinical utility. Because the fluid is typically discarded, it would take little effort to send for cytology. If the findings are negative in the setting of clinical suspicion, the workup should be continued (to include biopsy or D&C, if indicated). However, if the fluid is positive for cancer, the diagnosis is made, and the patient is spared a second costly and potentially uncomfortable procedure. Even if this scenario occurs in only 33% of women with cancer, it may be worth it. This sensitivity might even improve in the setting of a different catheter system or patient population.

Regarding the patients' preferences, van Dongen et al²⁴ compared SIS with office hysteroscopy and concluded that although SIS was less painful, most of the women preferred office hysteroscopy.

In conclusion, most women can feasibly undergo SIS and have the fluid sent for adequate analysis. However, the sensitivity is too low to routinely recommend as a diagnostic test at this time. Further refinement of the technique, potentially with different catheters, different injection rates, or different fluid sampling methods might improve this test. Although we were unable to identify any particular variables that were associated with improved sensitivity, this study may have been too small to adequately tease out such factors. It is possible that particular patient or tumor selection criteria could improve these results. We believe that future research should focus on defining the appropriate place for SIS cytology testing in the workup of patients at risk for endometrial cancer. Patients with positive cytology could then avoid other procedures, whereas those with concerning findings and negative cytology could be sent for further evaluation and biopsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1.
A, 58-year old patient with endometrial cancer revealed as a long, bulky mass. B, longitudinal view. C, transverse view.

TABLE 1

Demographic features of the patients

	n	%
Biopsy histology		
Endometrioid adenocarcinoma	23	76.67
Papillary serous adenocarcinoma	3	10
Adenosquamous type	1	3.33
Adenocarcinoma, NOS	3	10
Diagnostic method		
Biopsy	21	70
Biopsy, D&C	2	6.67
D&C	3	10
D&C, hysteroscopy	3	10
SIS, biopsy	1	3.33
Highest grade		
1	20	66.67
2	5	16.67
3	4	13.33
NA	1	3.33

NA, Not available; NOS, not otherwise specified.

TABLE 2

Cancer positivity in SIS samples within adequate sample conditions

Test	n	No. Cancer-Positive	Proportion, %	95% CI
5-mL initial flush	19	5	26	9–51
Adequate SIS	22	8	36	17–59
Total (either test positive)*	30	10	33	17–53

* Proportion of cancer positive out of the whole study sample.

TABLE 3

Logistic regression analysis (adequate samples)

Parameter	OR	95% CI	P
Diagnostic method (invasive)			
D&C vs biopsy	0.34	0.01–4.53	0.689
Hysteroscopy vs biopsy	1.27	0.01–111.99	1
SIS vs biopsy	1.13	0.03 to infinity	0.941
Highest grade			
2 vs 1	0.3	0.01–4.11	0.613
3 vs 1	2.19	0.09–151.42	1
Age	1.11	0.98–1.31	0.129
BMI	0.91	0.8–1.02	0.122
Volume instilled	0.95	0.88–1.02	0.158
Volume aspirated	0.92	0.57–1.45	0.772

OR, Odds ratio.