

ORIGINAL RESEARCH ARTICLE

Endometrial sampling before or after saline contrast sonohysterography in women with postmenopausal bleeding (ESPRESSO trial): A multicenter randomized controlled trial

Albertine J. Vroom^{1,2}  | Luca Aerts² | Marlies Y. Bongers^{1,2} | Arianne C. Lim² | Bart J. Pielkenrood³  | Peggy M. A. J. Geomini¹ | Nehalennia van Hanegem⁴

¹Department of Gynecology and Obstetrics, Maxima Medisch Centrum, Veldhoven, The Netherlands

²Department of Obstetrics and Gynecology, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands

³Department of Imaging and Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

⁴Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence

Albertine J. Vroom, Maastricht UMC+, GROW School for Oncology and Developmental Biology, P. Debyealaan 25, 6229 HX, Maastricht, The Netherlands.
Email: ajvroom@gmail.com

Abstract

Introduction: The aim of this study is to evaluate the quality of the endometrial sample obtained by office endometrial aspiration when performed before or after saline contrast sonohysterography (SCSH) in women with postmenopausal bleeding and a thickened endometrium. To conduct a complete, minimally invasive and cost-effective diagnostic workup in women with postmenopausal bleeding and a thickened endometrium, ideally both the office endometrial sampling and SCSH are performed. However, it is not known whether both tests affect each other when performed one after another.

Material and methods: Women with postmenopausal bleeding and an endometrial thickness >4 mm were eligible. Women were randomized into two groups: one group received endometrial aspiration before SCSH, the other group received SCSH before endometrial aspiration. The primary outcome was the proportion of sufficient endometrial samples. Reliability of the SCSH images and pain during procedures were secondary outcomes.

Results: During the inclusion period, 513 eligible women with postmenopausal bleeding visited the participating hospitals, 293 of whom received information about the study. Of these women, 232 (79%) agreed to participate. In the SCSH-aspiration group, 65 women (59%) had a sufficient endometrial sample compared with 70 (67%) in the aspiration-SCSH group (odds ratio 1.46, 95% CI 0.83-2.54, $P = .19$). The proportion of reliable sonographic images was significantly higher in the SCSH-aspiration group ($n = 88$, 87%) compared with the aspiration-SCSH group ($n = 71$, 74%) (OR 2.38, 95% CI 1.38-4.99, $P = .02$) in the per protocol analysis.

Conclusions: This study shows that the quality of an endometrial sample in women with postmenopausal bleeding is not affected by SCSH. Both procedures can be performed in one outpatient visit to perform an optimal diagnostic workup.

Abbreviations: NRS, numeric rating scale; OR, odds ratio; PMB, postmenopausal bleeding; PP, per protocol; SCSH, saline contrast sonohysterography; VAS, visual analogue scale.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Acta Obstetrica et Gynecologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Nordic Federation of Societies of Obstetrics and Gynecology (NFOG).

KEYWORDS

biopsy, endometrial neoplasms, postmenopausal bleeding, postmenopause, saline contrast sonohysterography, ultrasound

1 | INTRODUCTION

Postmenopausal bleeding (PMB) is a common complaint in daily gynecological practice and can be a sign of a malignant condition. Conventional transvaginal ultrasound should be performed in all women with PMB to measure endometrial thickness and stratify those with a high risk vs a low risk of endometrial malignancy.¹ In women with PMB and an endometrial thickness of more than 4 mm, further diagnostic workup is indicated.¹ Diagnostic workup should contain endometrial sampling and contrast sonography and/or diagnostic hysteroscopy to detect focal lesions. Office endometrial sampling is an accurate and minimally invasive method to detect endometrial (pre) malignancies with a reported sensitivity of 90%-100%, but focal lesions such as polyps can be missed.^{2,3} Endometrial (pre)malignancies can start as a diffuse lesion in the endometrial cavity or as a focal lesion in a polyp. The reported risk of a (pre) malignancy inside a polyp is up to 6% and for this reason it is advised to detect and remove endometrial polyps in women suffering from PMB.^{3,4}

Saline contrast sonohysterography (SCSH) is a minimally invasive and accurate method to detect polyps in women with PMB and could be used in the diagnostic workup in women with PMB and a thickened endometrium.⁵ Hysteroscopy is also an accurate method to detect polyps in women with PMB, but it is more invasive and more expensive than SCSH.^{6,7}

To perform a complete, minimally invasive, and cost-effective diagnostic workup, both office endometrial sampling and SCSH can be performed in a single outpatient visit in women with PMB and a thickened endometrium. However, it is not known whether both tests affect each other when performed one after another. In women with postmenopausal bleeding, 69% of the samples were reported as sufficient in previous research.² The quality of the endometrial samples is determined by the sufficiency of the sample. A previous study in predominantly premenopausal women, by Bij de Vaate et al⁸ found that the quality of the endometrial sample was affected by the SCSH. It is unclear, however, whether the same conclusion applies to postmenopausal women.

In view of this knowledge gap, we performed a multicenter, randomized controlled trial to investigate the quality of the endometrial sample obtained by office endometrial sampling when performed before or after SCSH in women with PMB and a thickened endometrium of more than 4 mm.

2 | MATERIAL AND METHODS

We performed a multicenter, randomized controlled trial with a parallel design in one university hospital and one teaching hospital

Key message

There was no significant difference in quality of the endometrial sample if aspiration was performed after saline contrast sonohysterography compared with endometrial samples taken before saline contrast sonohysterography. Both procedures can be performed within the same outpatient visit.

in the Netherlands. All details are described in the published study protocol.⁹

2.1 | Inclusion criteria

All women with PMB (bleeding >12 months after the last menstruation), and an endometrial thickness of more than 4 mm seen on transvaginal ultrasound were eligible for the trial. Exclusion criteria for this trial were the use of hormone replacement therapy, use of an anti-estrogen, or the presence of a cervical malignancy.

2.2 | Recruitment procedure

Women who visited either of the two hospitals with postmenopausal bleeding, without exclusion criteria, were counseled for the trial. Before their visit the women were informed by means of a patient information form and they were counseled about the trial during the outpatient visit. After transvaginal ultrasound, the treating physician—either a gynecologist or a fully authorized gynecologist in training—decided whether women were eligible, based on the endometrial thickness. When a woman with PMB had an endometrial thickness of more than 4 mm, verbal informed consent was obtained and the patient was asked to sign a written informed consent form after the procedure. After verbal consent, randomization was performed.

2.3 | Randomization procedure

Randomization took place using a sealed envelope. We randomized women into two groups. Both groups underwent endometrial sampling using a Pipelle[®] device (Pipelle de Cornier) and SCSH using an SCSH-catheter (Echosampler, Gynetics Medical devices). The order of the two procedures was randomized, using block randomization with alternating blocks and a 1:1 allocation.

One group underwent endometrial sampling followed by SCSH, the other group underwent SCSH and subsequently endometrial sampling. We performed both procedures directly after each other in one outpatient visit.

2.4 | Procedure

Office endometrial sampling was performed by inserting the Pipelle® device through the cervical canal and advancing it up to the fundus. In the next step the plunger was withdrawn followed by the withdrawal of the whole device to the lower uterine segment while making a corkscrew twisting movement. The Pipelle® device was emptied in a container with formalin by pushing the plunger back upwards. If the physician, performing the procedure, assessed the amount of tissue collected macroscopically as insufficient, the sampling was repeated with the same device without touching the formaldehyde when the physician emptied the Pipelle® device. The number of attempts to receive sufficient tissue was recorded. The SCSH was performed by inserting the SCSH catheter through the cervical canal, passing the internal os. The saline-filled syringe was applied to the connector and the transvaginal transducer was inserted. Ultrasound images were taken with simultaneous instillation of the saline solution. A cervical dilator (Os Finder; Cooper Surgical) was used in case of stenosis of the ostium.

2.5 | Data collection

Patient characteristics (age, body mass index, diabetes mellitus, hypertension, parity, medication, time since menopause, endometrial thickness in mm) and intervention details were recorded.

The physician recorded the presence or absence of a focal lesion on SCSH in the patient's file. In the case of a failed procedure, the physician recorded which procedure had failed and why. In addition, during the procedures, visual analogue scale (VAS) and/or numeric rating scale (NRS) scores were recorded. VAS was recorded using a VAS measuring rod which the woman held in their hands. On specific moments, the physician asked the woman for the VAS on the measuring rod: during the procedure, in between the procedures and after the procedures. The same procedure was followed with the NRS, only a number from 1 to 10 was asked, in which 0 means no pain and 10 the most awful pain imaginable. Data were collected using a case report form and the patient medical file.

2.6 | Outcomes

The primary outcome was the proportion of sufficient endometrial samples. We chose this outcome because we were interested in the quality of the endometrial sample and whether it would be

affected by the SCSH. In previous studies, the diagnostic accuracy has been researched thoroughly in cases where sufficient samples were obtained.¹ The in-house pathologists used standard protocol methods to assess the endometrial sample as sufficient or insufficient for diagnosis. To assess the sufficiency of the sample, the pathologist evaluated the presence and amount of endometrial tissue, stromal tissue and glands and also the context of the stromal and epithelial tissues. To ensure that the pathologist was blinded to the order of the procedure, the outcome of the SCSH was recorded first in all medical files.

As a secondary outcome, it was assessed whether the reliability of the sonographic images of the SCSH was influenced by the order of the procedures. During the trial, one of the trial centers (Maxima Medisch Centrum) had a large-scale data storage problem and the captured images of multiple included women were erased. Therefore, images could not be assessed by a blinded gynecologist. We decided to use the recorded diagnosis of the physician who performed the procedure for our secondary outcome measurement. The SCSH procedure was reported as "reliable" when the physician was able to record the absence or presence of a focal lesion.

Furthermore, we explored the incidence and intensity of the pain during and after the different procedures using NRS and/or VAS to determine which procedure was more painful and whether the order of procedure had any influence on the pain experience. Lastly, we investigated the incidence of failed procedures, combined with the reason for failure.

2.7 | Statistical analyses

The sample size was determined using data from previous studies.^{8,10} A difference in sufficient endometrial samples of 20% between both groups was assumed, 49% and 69% in the SCSH-aspiration group and aspiration-SCSH group, respectively. With a power of 80% and α of 5%, 98 women in each group were required. Considering a drop-out rate of 15% due to failed procedures, 116 women had to be included in each group.¹¹

Baseline characteristics were reported as mean with standard deviation for normally distributed variables or as median with interquartile range for non-normally distributed variables, or with absolute numbers and percentages for categorical data. As this is a randomized study, baseline characteristics were not tested for imbalance. Pain intensity during procedures was categorized as mild/moderate pain (NRS/VAS <4) or severe pain (≥ 4).¹² The proportion of women with a sufficient endometrial sample, the reliability of the SCSH, and pain during procedures were compared between the two study groups in an intention-to-treat analysis, using chi-squared test, and an odds ratio (OR), only excluding women who were ineligible for the study. In addition, a per protocol (PP) analysis was performed, excluding women in whom one or both procedures could not be performed. For statistical analysis, the Statistical Package for the Social Sciences (IBM Corp) version 24.0 was used. Statistical significance was set at $P < .05$.

2.8 | Ethical approval

The Medical Ethics Committee of the Máxima Medisch Centrum (Máxima MC) in Veldhoven gave approval on 29 March 2016 to execute this study in the Máxima MC and in the Maastricht Universitair Medisch Centrum (Maastricht UMC+), no. IRB W16.016. The study protocol is registered in the Dutch trial register NTR5690.

3 | RESULTS

Enrollment started in April 2016 and the last woman was included in December 2018. Of the 513 eligible women, 232 women were included. Of the remaining eligible women, 220 were missed for inclusion through a screening failure because of logistic reasons and 61 women refused participation (Figure 1). After randomization, five women in the SCSH-aspiration group and 12 women in the aspiration-SCSH group were excluded because they used hormone replacement therapy. In 18 of the 215 women (8%), one or both procedures could not be performed. In 10 women, neither procedure was performed, all as a result of cervical stenosis or severe pain during insertion of the first device. In three women, the SCSH was not possible and in five women the aspiration was not possible, all as a result of painful insertion of one of the devices. These women were excluded from the PP analysis. The remaining 197 women were included in the analysis. Baseline characteristics are presented in Table 1; Table 2 shows the findings during examination. In cases with insufficient aspiration samples, pathology results of biopsies during hysteroscopy, performed outside the scope of this trial, were recorded in Table 2.

TABLE 1 Baseline characteristics

	SCSH-aspiration (n = 111)	Aspiration-SCSH (n = 104)
Age, median (IQR)	58 (54-68)	59 (55-66)
BMI (kg/m ²), median (IQR)	28.4 (24.2-33.9)	29.4 (25.8-33.7)
Parity, median (IQR)	2 (1-3)	2 (2-3)
Vaginal birth	2 (2-3)	2 (2-3)
Months postmenopausal		
Median (IQR)	51 (19-187)	79 (21-162)
Missing, n (%)	14 (13)	6 (6)
Comorbidities, n (%)		
Diabetes	6 (5)	8 (8)
Hypertension	43 (39)	48 (46)
Medication use, n (%)		
Antihypertensive drugs	46 (41)	43 (41)
Anticoagulation drugs	9 (8)	15 (14)
Diabetic drugs, n (%)		
Insulin	2 (2)	1 (1)
Other medication	48 (43)	45 (43)

Note: Percentages may not add up to 100% due to rounding.

Abbreviations: BMI, body mass index; IQR, interquartile range; SCSH, saline contrast sonohysterography.

3.1 | Primary outcome

In the intention-to-treat analysis, 65 of 111 women (59%) in the SCSH-aspiration group had a sufficient endometrial sample, compared with 70 of 104 women (67%) in the aspiration-SCSH group

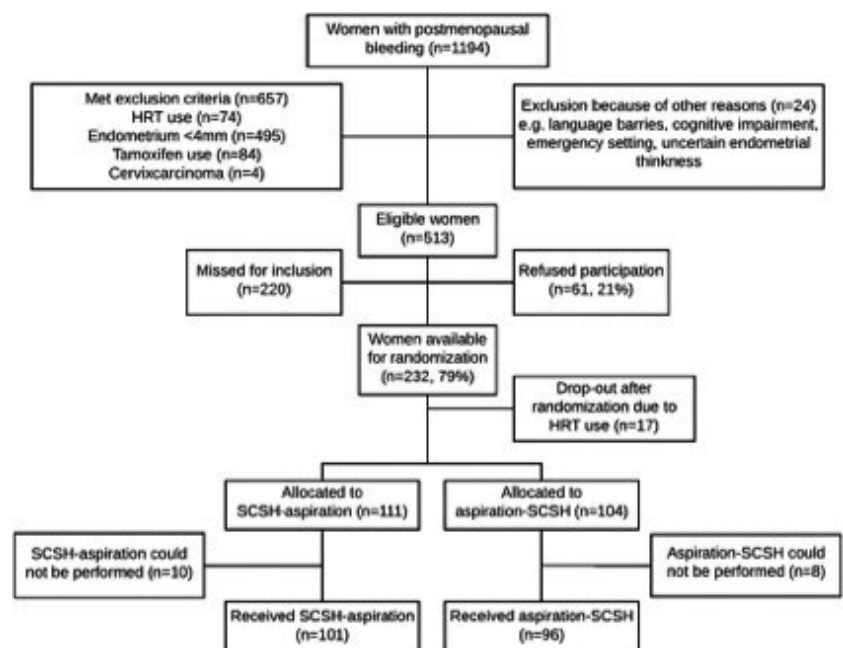


FIGURE 1 Flowchart of inclusion and treatment allocation. HRT, hormone replacement therapy; SCSH, saline contrast sonohysterography

TABLE 2 Findings during examination

	SCSH-aspiration (n = 111)	Aspiration-SCSH (n = 104)
Examination		
TED (mm), median (IQR)	8.0 (6.0-12.0)	7.4 (5.6-11.0)
Cavity length (cm), median (IQR)	7.0 (6.2-7.9)	7.0 (5.9-7.5)
Uterine position, n (%)		
AVF	80 (72%)	68 (65%)
RVF	18 (16%)	15 (14%)
Mid-position	12 (11%)	21 (20%)
Pathology, n (%) ^a		
Polyps	45 (41)	37 (36)
Malignancy	8 (7)	12 (12)
Pre-malignancy	2 (2)	3 (3)
Benign	49 (44)	46 (44)
Other	7 (6)	6 (6)

Note: Percentages may not add up to 100% due to rounding.

Abbreviations: AVF, anteversion flexion; IQR, interquartile range RVF, retroversion flexion; SCSH, saline contrast sonohysterography; TED, total endometrial thickness.

^aIn the 74 patients with an insufficient sample, pathology results of biopsy during hysteroscopy were used.

(OR 1.46, 95% CI 0.83-2.54, $P = .19$). In the PP analysis, 65 of 101 women (64%) in the SCSH-aspiration group had a sufficient endometrial sample compared with 70 of 96 women (73%) in the aspiration-SCSH group (OR 1.49, 95% CI 0.81-2.73, $P = .20$).

3.2 | Secondary outcome

In the intention-to-treat analysis, 88 of 111 women (79%) in the SCSH-aspiration group had SCSH images that were considered reliable, compared with 71 of 104 women (68%) in the aspiration-SCSH group (OR 1.78, 95% CI 0.96-3.30, $P = .07$). In the PP analysis, 88 of 101 women (87%) in the SCSH-aspiration group had SCSH images that were considered reliable, compared with 71 of 96 women (74%) in the aspiration-SCSH group (OR 2.38, 95% CI 1.38-4.99, $P = .02$). Hence, the proportion of reliable images was significantly higher in the SCSH- aspiration group in the PP analysis, but not in the intention-to-treat analysis.

Median pain score was 4 (interquartile range 1-6) during SCSH and 6 (interquartile range 3-8) during aspiration. Pain scores were comparable between the two groups. Furthermore, the proportion of women who perceived severe pain (NRS/VAS ≥ 4) during the aspiration or SCSH was comparable between both groups. In the SCSH-aspiration group, 69 women (73%) perceived severe pain during aspiration, compared with 72 women (77%) in the aspiration-SCSH group (OR 1.23, 95% CI 0.64-2.38, $P = .53$). In the SCSH-aspiration group, 52 women (54%) perceived severe pain during SCSH,

compared with 45 women (48%) in the aspiration-SCSH group (OR 1.23, 95% CI 0.70-2.18, $P = .47$).

The proportion of women in whom more than one aspiration was performed, was significantly higher in the SCSH-aspiration group ($n = 59$, 58%) than in the aspiration-SCSH group ($n = 32$, 35%) (OR 2.63, 95% CI 1.47-4.72, $P < .01$).

In total, 25 suboptimal SCSH procedures were observed in the included women ($n = 25$, 13%). In most of these, the achieved distension was suboptimal ($n = 19$, 76%). The proportion of women with suboptimal SCSH due to lack of distension was similar in both groups. Ultrasound visualization was difficult because of the position of the uterus in three cases and because of increased echogenicity during the procedure in two cases. One woman (4%) found SCSH to be too painful and therefore the gynecologist terminated the procedure prematurely, aspiration was already performed.

4 | DISCUSSION

The main finding of this randomized trial was that the quality of the endometrial sample was not affected by whether SCSH was performed before or after endometrial sampling, as we did not find a difference of 20% or more in number of sufficient samples between both groups. We conclude that it is possible to perform both the endometrial aspiration and the SCSH in one outpatient visit without diminishing the quality of the tissue sample.

The present study shows that the reliability of the SCSH was lower when performed after the endometrial aspiration in the PP analysis. This could be clinically relevant and can be explained by the fact that the endometrium is impaired by the aspiration and therefore the endometrial lining is harder to distinguish by ultrasound. In addition, the impaired endometrium could mimic a focal pathology such as a polyp. As there was no difference in perceived pain between the two groups, the order of procedures did not influence pain intensity.

Bij de Vaate et al performed a randomized study to evaluate the quality of the endometrial sample obtained before or after SCSH from a group of mostly premenopausal women ($n = 93$, 85%). Our results are not in accordance, as the study of Bij de Vaate showed a significantly lower quality of the endometrial sample when performed after SCSH.⁸ The premenopausal status could influence the findings, as the endometrium in premenopausal women is histologically different to that in postmenopausal women and the incidence of different types of endometrial pathology is linked to menopausal status. Furthermore, the expected diagnosis in premenopausal women with abnormal bleeding is different compared with postmenopausal women. For example, women with PMB have a higher risk of an endometrial malignancy, which could affect the amount of tissue in the endometrial sample.

We included only women with PMB to answer this research question in this specific group of women. The percentages of polyps and (pre)malignancies, as described in Table 2, were comparable to previous epidemiological data and therefore show

a representable group of postmenopausal women.¹ In the SCSH-Aspiration group, eight malignancies (7%) were found, whereas in the Aspiration-SCSH group 12 malignancies (12%) were found. This difference is most likely due to chance; however, a lower detection rate due to a higher proportion of insufficient samples in the first group could not be ruled out based on our data. As stated in the results, women with a suboptimal SCSH were included in the analyses. In these women, saline was infused, and therefore the endometrium could have been affected, so these women were still eligible for our primary outcome.

With the results of this study, we conclude that it is possible to perform both procedures in one outpatient visit, as the quality of the endometrial sample is not significantly affected by the SCSH. The advantage of performing both procedures in the same session is that the diagnostic workup is better compared with a workup with an endometrial sample alone. It may be considered to perform SCSH first, as our secondary outcome shows that the reliability of SCSH images is lower when endometrial aspiration is performed before SCSH. However, it is worth mentioning that this difference was only found in the PP analysis.

As it is possible that the first aspirations will contain saline from the previous procedure, macroscopic assessment of the amount of tissue that is aspirated during the procedure should be considered, with subsequent repeat sampling if necessary. Our study showed that the proportion of women in whom more than one aspiration was performed was higher in the SCSH-aspiration group than in the aspiration-SCSH group. This could be explained by the fact that in the first attempt mostly saline used for the SCSH is aspirated and could also be explained by the relatively small volume of the cannula of the Pipelle[®] device.

The proportion of failed procedures was lower than reported in previous literature. In 8% of the randomized women, one or both of the procedures failed, mostly as a result of cervical stenosis. In previous literature, the proportion of failed procedures was 13%-20% for the SCSH and 11% for the aspiration.^{2,13,14} In the majority of these cases cervical stenosis was the reason for the failed procedure, for both SCSH and endometrial sampling. The use of a cervical dilator in our daily practice could be the explanation of a smaller proportion of failed procedures due to cervical stenosis. The median pain scores reported in our study are similar to pain scores reported in previous literature.¹⁵

This is the first, randomized controlled trial to analyze the quality of the endometrial sample when performed before or after SCSH in women with postmenopausal bleeding. This study included a large group of women with postmenopausal bleeding, so sufficient statistical power was achieved.

An important limitation is the fact that the SCSH images were assessed by a non-blinded physician who assessed the images during the procedure. This possibly influences the interpretation and therefore our results of this secondary outcome measurement. Although we did find a difference in reliability of the SCSH between the groups in the PP analysis, this outcome is less reliable, because this study is not powered for this secondary outcome.

Of the 513 eligible women, 281 women were not included. At least 61 women refused participation. It is possible that a substantial part of the remaining 220 women would have refused participation but refusal was not recorded, because these women were not informed of the study. This could be a limitation, as we could not determine the characteristics of these women.

5 | CONCLUSION

This study shows that the quality of an endometrial sample in women with PMB is not affected by SCSH. Both procedures can be performed in one outpatient visit to perform an optimal diagnostic workup.

CONFLICT OF INTEREST

None.

ORCID

Albertine J. Vroom  <https://orcid.org/0000-0002-4782-1805>

Bart J. Pielkenrood  <https://orcid.org/0000-0003-4701-3311>

REFERENCES

- van Hanegem N, Breijer MC, Khan KS, et al. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. *Maturitas*. 2011;68:155-164.
- van Hanegem N, Prins MMC, Bongers MY, et al. The accuracy of endometrial sampling in women with postmenopausal bleeding: a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2016;197:147-155.
- van Hanegem N, Breijer MC, Slockers SA, et al. Diagnostic workup for postmenopausal bleeding: a randomised controlled trial. *BJOG*. 2016;124:231-240.
- Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. *Obstet Gynecol*. 2010;116:1197-1205.
- Vroom AJ, Timmermans A, Bongers MY, van den Heuvel ER, Geomini PMAJ, van Hanegem N. Diagnostic accuracy of saline contrast sonohysterography in detecting endometrial polyps in women with postmenopausal bleeding: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2019;54:28-34.
- Clark TJ, Bakour SH, Gupta JK, Khan KS. Evaluation of outpatient hysteroscopy and ultrasonography in the diagnosis of endometrial disease. *Obstet Gynecol*. 2002;99:1001-1007.
- Carlos RC, Bree RL, Abrahamse PH, Fendrick AM. Cost-effectiveness of saline-assisted hysterosonography and office hysteroscopy in the evaluation of postmenopausal bleeding: a decision analysis. *Acad Radiol*. 2001;8:835-844.
- Bij de Vaate AJM, van Doorninck CEM, Visser M, van der Slikke JW, Brolmann HAM. Endometrial aspiration before or after saline infusion sonography and the effect on specimen quality: a randomized study. *J Minim Invasive Gynecol*. 2008;15:580-583.
- Vroom AJ, Prins MM, Bongers MY, Geomini PM, Timmermans A, van Hanegem N. Endometrial Sampling before or after Saline infusion Sonography (ESPRESSO Trial): a national survey and a study protocol of a multicenter RCT. *Minerva Gynecol*. 2017;69:304-308.
- Brölmann HAM, Bongers MY, Moret E, Smeets N, Bremer GL, Dijkhuizen FPHLJ. Transvaginale contrastechoscopie van de uterus in de diagnostiek van abnormaal uterinen bloedverlies:

- Minder hysteroscopieën nodig [Transvaginal contrast sonography of the uterus in the diagnosis of abnormal uterine blood loss: less hysteroscopies needed] (in Dutch). *Ned Tijdschr Geneeskd.* 2003;147:502-506.
11. Epstein E, Ramirez A, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand.* 2001;80:1131-1136.
 12. Oldenmenger WH, de Raaf PJ, de Klerk C, van der Rijt CCD. Cut points on 0-10 numeric rating scales for symptoms included in the Edmonton Symptom Assessment Scale in cancer patients: a systematic review. *J Pain Symptom Manage.* 2013;45:1083-1093.
 13. de Kroon CD, Jansen FW, Trimbos JB. Doelmatigheid van water-contrastechografie ter beoordeling van het cavum uteri [Efficiency of saline contrast hysterosonography for evaluating the uterine cavity] (in Dutch). *Ned Tijdschr Geneeskd.* 2003;147:1539-1544.
 14. Epstein E, Ramirez A, Skoog L, Valentin L. Transvaginal sonography, saline contrast sonohysterography and hysteroscopy for the investigation of women with postmenopausal bleeding and endometrium >5 mm. *Ultrasound Obstet Gynecol.* 2001;18:157-162.
 15. Van den Bosch T, Verguts J, Daemen A, et al. Pain experienced during transvaginal ultrasound, saline contrast sonohysterography, hysteroscopy and office sampling: a comparative study. *Ultrasound Obstet Gynecol.* 2008;31:346-351.

How to cite this article: Vroom A J., Aerts L, Bongers M Y., et al. Endometrial sampling before or after saline contrast sonohysterography in women with postmenopausal bleeding (ESPRESSO trial): A multicenter randomized controlled trial. *Acta Obstet Gynecol Scand.* 2021;100:1258-1264. <https://doi.org/10.1111/aogs.14086>