

Title Page

Title:

Prevalence of contrast intravasation in HyCoSy/HyFoSy. Results of a multicenter study and systematic review of the literature with meta-analysis.

Type Manuscript: Original research

Running title: Uterine intravasation frequency is related to contrast agent

Authors

Juan Luis Alcazar¹, Laura Peñate², Virginia Casanova³, Clara Piera⁴, Virginia Engels⁵, Margarita Medina⁶, Cristina Ros⁷, Laura Sotillo⁵, Eugenia Antolín⁵, Irene Pelayo⁸, Carmina Bermejo⁹, María Ángela Pascual¹⁰, Betlem Graupera¹⁰, Silvia Ajossa¹¹, Stefano Guerriero¹¹.

¹ Department of Obstetrics and Gynecology, Hospital QuirónSalud, Málaga, Spain

² Department of Obstetrics and Gynecology, Torrejon University Hospital, Torrejon de Ardoz, Spain

³ Department of Obstetrics and Gynecology, Hospital Virgen de la Luz, Cuenca, Spain

⁴ Department of Obstetrics and Gynecology, Hospital Denia, Denia, Spain

⁵ Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Hospital Universitario La Paz. IdiPAZ Madrid, Spain

⁶ Department of Obstetrics and Gynecology, Hospital Universitario Materno-Infantil, Las Palmas de Gran Canaria, Spain

⁷ Department of Gynecology, Institut Clínic de Ginecologia, Obstetrícia, i Neonatologia, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

⁸ Department of Obstetrics and Gynecology, Hospital Universitario Ramón y Cajal, Madrid, Spain

⁹ Delta Ecografía, Madrid, Spain.

¹⁰ Department of Obstetrics, Gynecology, and Reproduction, Hospital Universitari Dexeus, Barcelona, Spain

¹¹ Centro Integrato di Procreazione Medicalmente Assistita (PMA) e Diagnostica Ostetrico-Ginecologica, Policlinico Universitario Duilio Casula, Monserrato, University of Cagliari, Cagliari, Italy.

Corresponding author:

Juan Luis Alcazar, MD, PhD

Department of Obstetrics and Gynecology. Hospital QuironSalud, Málaga.

Avenida Imperio Argentina 1, 29004, Málaga, Spain

Tel +34-951-940000 Email: jalcazar@unav.es

ABSTRACT

Objective: To determine the frequency of uterine contrast agent intravasation during HyCoSy/HyFoSy for assessing tubal patency in infertile women.

Methods: Prospective observational multicenter study performed in nine European university hospitals, comprising a series of non-consecutive women who underwent HyFoSy (ExEm™ foam) for tubal patency assessment in the context of infertility between May 2016 and December 2022. All examinations were performed using the same scanning protocol. In addition, a systematic review of literature using database search (Pubmed, Scopus and Web of Science) of articles published between January 2000 and March 2024 evaluating the presence of venous contrast intravasation during HyCoSy/HyFoSy for assessment of tubal patency in infertile women. Pooled prevalence for intravasation was estimated. Heterogeneity was assessed by calculating I^2 . Quality of studies was assessed using the Newcastle-Ottawa scale.

Results: Prospective study: 1946 women were recruited. Intravasation was observed in 12 cases (0.6%, 95% CI: 0.5%-0.9%). The frequency of intravasation was similar in seven centers, ranging from 0% to 0.7%. In two centers the frequency observed was higher, 2.6% and 3.0%, respectively. No significant patient reaction or complication was observed in those 12 women with intravasation. In addition, the search identified 74 studies. After exclusions, 11 articles (9 using SonoVue™ and 2 using ExEm™ foam) were included, comprising data from 5028 women. Pooled prevalence for contrast intravasation was significantly higher for SonoVue™ (23.0%, 95%CI: 19.0%-27.0%) than for ExEmFoam (7.0%, 95%CI: 5.0%-9.0%). Heterogeneity was high (I^2 : 91.8%). Studies quality was good.

Conclusion: Uterine intravasation is less frequent using ExEm™ foam than SonoVue™.

Keywords: Intravasation, uterine, contrast agents, hysterosonopalpingography

MAIN TEXT

INTRODUCTION

Assessment of tubal patency in women with reproductive problems is an essential part of the workup for infertile couples. Approximately 35% of women with infertility present some tubal alteration (1). Laparoscopic examination, the tubal chromoperturbation dye test (LDT) and X-ray hysterosalpingography (HSG) are accepted as the gold standard for that purpose (2). Two-dimensional (2D) hysterosalpingo-contrast-sonography (HyCoSy) has been proposed as alternative to LDT and HSG (3). This technique is well tolerated and easily performed (4). Currently, *SonoVueTM* is one of the most used contrast agents in HyCoSy. This is a second-generation ultrasound contrast, consisting of a suspension of stabilized sulfur hexafluoride (SF6) microbubbles that provide high resistance and durability (5). However, the intrauterine and tubal use of this agent is off label (6). In 2007, a non-embryotoxic gel was introduced as an intrauterine medium for HyCoSy as an alternative to previously mentioned contrast. The so-called *ExEm-foamTM* contains hydroxyethylcellulose and glycerol and its instillation offer a more stable filling of the uterine cavity (7). Both contrasts have been proven to be very well tolerated in terms of pain (8). However, related to HyCoSy or HyFoSy, a particular phenomenon has been described, the intravasation of contrast into the uterine venous vessels (9-11). The clinical significance of this phenomenon is not known. However, several papers have been reported describing contrast intravasation during HyCoSy /HyFoSy. In this study, we aimed to assess the frequency of venous contrast intravasation during HyFoSy and the potential factors associated to this phenomenon. In addition, we aimed to perform a meta-analysis pooling data from studies that have reported venous intravasation during HyCoSy/HyFoSy.

METHODS

Current study

This is a prospective observational multicenter study performed in nine European university hospitals (eight in Spain and one in Italy), comprising a series of non-consecutive women who underwent HyFoSy for tubal patency assessment in the context

of infertility between May 2016 and December 2022. IRB approval was obtained in all participating centers.

All examinations were performed using the same scanning protocol and ultrasound evaluation were done by expert examiners (12). Briefly, HyFoSy procedures were scheduled in the late follicular period (day 7–11 of the menstrual period). Antibiotic prophylaxis with 1 g of oral azithromycin was given to all the patients the night before the examination in most centers. In order to make the uterine catheterization easier straightening the utero-cervical angle, patients were told to come with a full bladder. The external cervical os was visualized using a vaginal speculum and cleaned with a 3% iodine povidone solution. Thereafter, the endocervix was cannulated with either a pediatric nasogastric tube, an 8F Foley's catheter, an intrauterine insemination catheter, or a specifically designed HyFoSy catheter. In very unfavorable cases, cervixes were gripped with reusable Pozzi forceps to favor the entrance. Foam was prepared by a nurse following the instructions of the manufacturer, by mixing 5 mL of ExEm-gel with 5 mL of purified water. The mixture of foam and air microbubbles was then transferred to a dosing syringe with through the coupling device of the ExEm™ kit.

The uterus was then scanned from horn to horn in the sagittal plane and from cervix to the fundus in the transverse plane. Correct intracavitary position of the catheter was ensured after having established a whole overview of the uterus. Ultrasound image was magnified in order to contain the uterine corpus and cervix. Sonographic image focused on the tip of the catheter. Foam was slowly injected via the catheter to assess patency of fallopian tubes. Sonographic probe was moved from horn to horn and fallopian tubes were evaluated during 5 -7 minutes since foam is stable and shows echogenicity during this lapse of time.

The observation of intravasation of contrast in the venous territory of the uterus was defined as the visualization of contrast agent penetrating the myometrium during the procedure (Figures 1 and 2). It was recorded as “present” or “not present”.

Data such as tubal patency (unilateral or bilateral), endometrial thickness, presence of uterine fibroids, presence of uterine adenomyosis, presence of uterine Mullerian anomaly, pain score during the procedure (visual analogue scale), type of catheter used and type of infertility (primary or secondary) were also recorded for further analysis as potential factors associated to venous intravasation.

The quantitative variables were tested for normal distribution using the Kolmogorov-Smirnov test. Descriptive data are presented as mean with standard deviation or median with interquartile range (IQR) for quantitative variables, depending on type of distribution, and number and percentage for qualitative variables. Quantitative variables were compared by one-way ANOVA test. Qualitative variables were compared using Mann-Whitney's U test. Statistical tests were two-sided and were performed with SPSS V.20 [IBM Inc., Chicago, IL, USA]. A p-value below 0.05 was considered significant.

Meta-analysis

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (www.prisma-statement.org) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13). The inclusion and exclusion criteria for the selection of studies, as well as how data extraction and quality assessment, were defined before the start of the search. Institutional Review Board approval was waived because of study's nature and design. We did not register the protocol.

The literature search we performed by three authors in three databases (PubMed, Scopus and Web of Science) between January 2000 and March 2024. No restrictions were set. We searched for primary prospective or retrospective observational studies reporting the presence of venous contrast intravasation during HyCoSy or HyFoSy for assessing of tubal patency in infertile women as single inclusion criterion. We used the following terms: "intravasation", "uterine", "tubal patency", "ultrasound", "ultrasonography".

Titles and abstracts of citations identified in the search were screened by three authors. Duplicated records were excluded. Reviews, letter-to-editor and studies not dealing with the investigated topic were also excluded. The reference list of included studies was reviewed to identify any additional relevant study. The corresponding author for a given study was contacted in cases of missing data. If no response was provided the study was also excluded.

Three authors extracted the following data from each study ultimately included: Publication year, country, study's design, recruitment period, number of patients included, number of patients exhibiting venous intravasation, definition of

intravasation, patients' mean age (with standard deviation or range), indication for HyFoSy/HyCoSy, type of contrast used, day of the cycle when HyFoSy/HyCoSy was performed, endometrial thickness when HyFoSy/HyCoSy was performed.

Pooled estimates of the frequency of venous intravasation with the corresponding 95% Coefficient intervals were calculated using the random effects model using the *prometan* command in STATA 14.0 software. Heterogeneity was assessed by calculating I^2 (14).

Quality of studies was assessed using the Newcastle-Ottawa scale (15). Two researchers made a qualitative assessment based on the domains of "Selection", "Comparability" and "Outcome". The Newcastle- Ottawa Scale, which is based on three main domains: "Selection," "Comparability" and "Outcome."9 "Selection" domain includes four items (representativeness of the exposed cohort, whether the non-exposed is drawn from the same community that the exposed cohort, ascertainment of the exposure and demonstration that the outcome of interest was not present at that start of the study. It can sum up to six stars). "Comparability" domain includes one item (comparability according to control for confounders. It can sum up to two stars). "Outcome" domain includes three items (assessment of the outcome, enough follow-up time and adequacy of follow up. It can sum up to five stars). The quality if the studies is scored as follows: Good quality (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain), Fair quality 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain), and Poor quality (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain). Disagreements were solved by discussion with a third researcher.

RESULTS

Current study

During study period, 1946 women were recruited. Patients' mean age was 34 years old, ranging from 22 years to 43 years. All women were evaluated during days 3 to 7 of the menstrual cycle.

Intravasation was observed in 12 cases (0.6%, 95% CI: 0.3%-0.9%). The frequency of intravasation was similar in seven centers, ranging from 0% to 0.7%. In two centers the

frequency observed was higher (2.6% and 3.0%, respectively). Because of the very low frequency of events observed, statistical analysis of potential factors associated to venous intravasation was precluded.

No significant patient reaction or complication was observed in those 12 women with intravasation.

Systematic Review and Meta-analysis

The search identified 74 studies. After exclusions, 13 articles that met inclusion criteria to be included. However, full text of two studies could not be obtained in spite of attempts to contact with the authors (9,10). Therefore, eleven studies comprising data from 5028 women were ultimately included (16-26). Figure 3 shows the flow diagram of studies' search and selection.

Table 1 shows the main characteristics of the studies included in this meta-analysis. Nine studies (all from China) used SonoVue™ as contrast agent (16-22,25,26) and two studies (both from Australia) used ExEm™ Foam as contrast agent (23,24). Eight studies were retrospective observational studies (17-23,25), two studies were prospective (16,24) and in one study's design was not stated (26).

Table 1. Main features of the studies included in the meta-analysis

Author	Year	Country	Study design	Contrast agent	Patient's age*	Cycle's day	Number centers	N observers	N	N intravasation
Wang	2018	China	Prospective	SonoVue	32.4±2.1	3-9	One	Two	276	36
He	2019	China	Retrospective	SonoVue	30.3±5.1	3-7	One	Two	455	124
Shi	2019	China	Retrospective	SonoVue	30.1±1.5	3-10	One	NA	643	169
Tian	2019	China	Retrospective	SonoVue	NA	NA	One	NA	1328	293
Sang	2020	China	Retrospective	SonoVue	NA	3-7	One	NA	306	45
Jin Y	2022	China	Retrospective	SonoVue	NA	3-10	One	Two	276	62
Jin BB	2022	China	Retrospective	SonoVue	31.4±4.6	3-7	One	One	399	63
Ford	2023	Australia	Retrospective	ExEm	34.3±4.6	NA	One	Two	436	30
Lo	2024	Australia	Prospective	ExEm	NA	NA	One	NA	52	6
Chen	2024	China	Retrospective	SonoVue	NA	3-7	One	NA	451	92
Yang	2024	China	NA	SonoVue	32.4±4.9	3-7	One	NA	416	162

NA: data not available. *Data expressed as mean ± standard deviation

Pooled prevalence for contrast intravasation was higher for SonoVue™ (23.0%, 95%CI: 19.0%-27.0%) than for ExEm™ Foam (7.0%, 95%CI: 5.0%-9.0%). However, the sample size was significantly lower in ExEm™ Foam studies (N=488 versus N= 4540).

Heterogeneity observed was high for studies using SonoVue™ (I^2 : 91.8%) (Figures 4 and 5).

Studies quality was considered as good by NOS assessment for all studies included (table 2).

Table 2. Quality assessment of studies included according to the Newcastle-Ottawa scale

Author	Year	Selection	Comparability	Outcome
Wang	2018	★★★★	★★	★★★
He	2019	★★★	★	★★★
Shi	2019	★★	★	★★★
Tiang	2019	★★	★	★★★
Sang	2020	★★	★	★★
Jin Y	2022	★★★	★★	★★★
Jin BB	2022	★★★	★	★★★
Ford	2023	★★★	★	★★★
Lo	2024	★★★★	★★	★★★
Chen	2024	★★	★	★★★
Yang	2024	★★★	★	★★★

DISCUSSION

Contrast intravasation is well-known phenomenon consisting of part of the intrauterine contrast agent diffusion into the uterine veins and/or myometrium through blood or lymphatic vessels during X-ray hysterosalpingography (27). It has been reported that intravasation may occur in 0.4%-7.2% of the cases when lipiodol-based x-ray hysterosalpingography (X-HSG) is performed (28,29).

With the advent of ultrasound-based contrast agents, hysterosono-contrast-salpingography (HyCoSy) has become a standard of care for tubal patency assessment in infertile women (30). Currently, two different ultrasound-based contrast agents are used in clinical practice. Namely, SonoVue™, usually referred as HyCoSy; and ExEm™ foam, usually referred as HyFoSy. As occurs with lipiodol-based X-HSG, contrast intravasation has been described when using ultrasound-based contrast agents (9,11). When happening using ultrasound-based contrast agent, intravasation is observed in real-time 2D ultrasound as a myometrial enhancement by the echogenic microbubbles

(23). In case of 3D or 4D ultrasound findings are related to “dendritic”, “mesh-like” or “mist-cloudy” image (22).

The clinical significance of this phenomenon is not well known. It has been reported that uterine intravasation might impair image quality leading to image misinterpretation and potentially causing false negative results (11,16). From the safety point of view, no apparent complications are directly related to this phenomenon, either for HyCoSy or HyFoSy. Only a single case of vasculitis has been reported related to this phenomenon in HyFoSy (31).

In our systematic review and meta-analysis, we observed that the frequency of intravasation was much lower for ExEm™ foam (7.0%) than for SonoVue™ (23%). However, it should be considered that the sample size of cases using ExEm™ foam (n=488) was 10-fold smaller than for SonoVue™ (n=4540). Therefore, a potential risk of underestimation of intravasation occurring during HyFoSy could exist. A possible explanation for this different frequency is that ExEm™ foam is more stable and the microbubble size is much larger than SonoVue™ (45.6-60.6 µm versus 2.5µm) and, therefore, ExEm™ foam could be less prone to diffuse into the uterine blood or lymphatic vessels.

Some studies have assessed which factors could be related to uterine intravasation when HyCoSy/HyFoSy is performed. Regarding the use of SonoVue™, several studies have observed that the probability of intravasation is higher when HyCoSy is performed in the early phase of the menstrual cycle (before the day 6) (16,18,21,26) and if endometrial thickness is less than 6mm (16,18,21,25,26). This phenomenon may happen more probably in case of previous intrauterine surgery (18,21,25,26), in cases of secondary infertility (18,21,25,26) and in cases of uterine adenomyosis (26). Factors such as tubal occlusion or patency during the procedure, past history of ectopic pregnancy and operator’s experience are controversial.

Related to ExEm™ foam, only one study assessed the factors associated to intravasation. Ford et al observed that intravasation was more frequent if HyFoSy is performed in women with endometrial thickness below 6mm. But it was not related to operator’s experience or adenomyosis (23).

However, in our present prospective study, we have observed that the frequency of ExEm™ foam contrast venous intravasation during HyFoSy was very low (0.6%). Much

lower than other studies using HyFoSy. Interesting to note is the fact that in seven out of the nine centers participating in the prospective study the frequency was below 1%. We do not have a clear explanation for this controversial finding. A potential explanation could be study design. Our study was prospective and examiners were aware of recording the presence on uterine intravasation. On the other hand, our study was multicenter and the sample size was larger than two studies found in the systematic review, which were both performed in the same single center, with a smaller sample size.

Our study has limitations. Related to the systematic review, we observed that only two studies assessed intravasation in HyFoSy, both of them from Australia, from the same institution, one was retrospective and with small size. On the other hand, regarding HyCoSy, all studies were performed in China and most of them were retrospective assessment of recorded images. This could introduce a potential source of bias as compared to real-time assessment done in prospective studies. Furthermore, the prevalence of uterine intravasation observed for SonoVue™ varied significantly across studies, from 13% to 39%, which explains the high heterogeneity observed. Therefore, data should be considered with caution. Regarding the prospective study, the main limitation was the very low prevalence of intravasation observed. This low prevalence makes unmeaningful the assessment of factors associated to this phenomenon.

In conclusion, according to our findings the probability of venous intravasation is lower when ExEm™ foam is used as compared to SonoVue™.

References

1. Dun EC, Nezhat CH. Tubal factor infertility: diagnosis and management in the era of assisted reproductive technology. *Obstet Gynecol Clin North Am* 2012;39:551–566
2. Saunders RD, Shwayder JM, Nakajima ST. Current methods of tubal patency assessment. *Fertil Steril* 2011; 95: 2171–2179.
3. Campbell S, Bourne TH, Tan SL, Collins WP. Hysterosalpingo contrast sonography (HyCoSy) and its future role within the investigation of infertility in Europe. *Ultrasound Obstet Gynecol.*1994; 4:245–253
4. Socolov D, Boian I, Boiculese L, et al. Comparison of the pain experienced by infertile women undergoing hysterosalpingo contrast sonography or radiographic hysterosalpingography. *Int J Gynecol Obstet.* 2010; 111: 256–259.
5. Chen SS, Chen SS, Du X, Chen Q, Chen SS. Combined real-time three-dimensional hysterosalpingo-contrast sonography with B mode hysterosalpingo-contrast sonography in the evaluation of fallopian tube patency in patients undergoing infertility investigations. *Biomed Res Int* 2019:9408141
6. Van Schoubroeck D, Van Den Bosch T, Meuleman C, Tomassetti C, D’Hooghe T, Timmerman D. The use of a new gel foam for the evaluation of tubal patency. *Gynecol Obstet Invest.* 2013; 75:152–156
7. Emanuel MH, Exalto N. Hysterosalpingo-foam sonography (HyFoSy): a new technique to visualize tubal patency. *Ultrasound Obstet Gynecol.* 2011;37:498–499
8. Boned-López J, Alcázar JL, Errasti T, et al. Severe pain during hysterosalpingo-contrast sonography (HyCoSy): a systematic review and meta-analysis. *Arch Gynecol Obstet.* 2021;304:1389-1398.
9. Guo J, Wang SS, Chen Q, et al. Analysis on the counter current of contrast medium in transvaginal real-time three-dimensional hysterosalpingo-contrast sonography. *Chin J Med Imaging Technol* 2014; 30:1063–1066.
10. Liang N, Wu QQ, Li JH, Gao FY, Guo CX, Tian Y. Analysis on the reasons of contrast agents reflux during transvaginal real-dimensional hysterosalpingo-contrast sonography. *Chin J Ultrasonogr* 2015; 24:797– 799.

11. Ludwin A, Ludwin I, Martins WP. Venous intravasation during evaluation of tubal patency by ultrasound contrast imaging. *Ultrasound Obstet Gynecol.* 2018; 51:143–145.
12. Engels V, Medina M, Antolín E, et al. Feasibility, tolerability, and safety of hysterosalpingo-foam sonography (hyfosalpingography). multicenter, prospective Spanish study. *J Gynecol Obstet Hum Reprod.* 2021;50:102004.
13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting—meta-analysis of observational studies in epidemiology (MOOSE) group B. *JAMA Neurol.* 2000; 283:2008–2012
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557-560
15. Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med.* 2015;8:2-10
16. Wang W, Zhou Q, Zhou X, Chen Z, Zhang H. Influence Factors on Contrast Agent Venous Intravasation During Transvaginal 4-Dimensional Hysterosalpingo-Contrast Sonography. *J Ultrasound Med.* 2018;37:2379-2385.
17. He Y, Wu H, Xiong R, et al. Intravasation Affects the Diagnostic Image Quality of Transvaginal 4-Dimensional Hysterosalpingo-Contrast Sonography With SonoVue. *J Ultrasound Med.* 2019;38:2169-2180.
18. Shi J, Li S, Wu H, et al. The Influencing Factors of Venous Intravasation During Transvaginal Four-dimensional Hysterosalpingo-contrast Sonography With SonoVue. *Ultrasound Med Biol.* 2019;45:2273-2280.
19. Tian H, Gao C, Yan P, et al. Impact factors of contrast agent venous intravasation during transvaginal four-dimensional hysterosalpingo-contrast sonography. *Chin J Interv Imag Ther.* 2019;16:612-625
20. Sang Y, Zhou X, Wang W, Mai Z, Deng K, Xie X. Analysis of the reasons of contrast agent venous intravasation during transvaginal four-dimensional hysterosalpingo-contrast sonography. *Chin J Ultrasoundography.* 2020;29:706-710.

21. Jin Y, Huang W, Qv Q, Liu S. Development of a Nomogram for Predicting Intravasation Before Transvaginal 4-Dimensional Hysterosalpingo-Contrast Sonography. *Int J Womens Health*. 2022;14:583-591.
22. Jin BB, Ma Y, Zhao XH, Teng YL, Zhu SY. Operator's Influence on Contrast Agent Intravasation During Hysterosalpingo-Contrast Sonography: Explanation Based on a Physics Model. *Int J Gen Med*. 2022;15:7709-7718.
23. Ford J, Hince D, Lee E, Lo G. Intravasation complicating hysterosalpingo-foam sonography (HyFoSy) using ExEm® Foam. *Aust N Z J Obstet Gynaecol*. 2023;63:577-582.
24. Lo G, Hince D, Johnson N, Hofman PL, Sekhon J, Lee E. Ultrasound-guided Lipiodol® hysterosalpingography: A prospective study on pregnancy and complication rates. *Aust N Z J Obstet Gynaecol*. 2024;64:326-333.
25. Chen M, Huang S, Song C, et al. Value of painless transvaginal four-dimensional hysterosalpingo contrast sonography in reducing venous intravasation: a comparative study. *J Ultrasound*. 2024;27:511-517.
26. Yang P, Zhong Y, Zhang C, Zhang Y, Fan X, Shi H. Contrast Agent Reflux in Transvaginal 4-D Hysterosalpingo-Contrast Sonography. Influencing Factors and Coping Strategies. *Ultrasound Quarterly* 2024;40: 61–65
27. Lindequist S, Justesen P, Larsen C, Rasmussen F. Diagnostic quality and complications of hysterosalpingography: Oil versus water-soluble contrast media: A randomized prospective study. *Radiology* 1991;179:69–74.
28. Nunley WC, Jr, Bateman BG, Kitchin JD, 3rd, Pope TL, Jr. Intravasation during hysteron-salpingography using using oil-base contrast agent: A second look. *Obstet Gynecol* 1987;70:309–312
29. Dusak A, Soydinc HE, Onder H, et al. Venous intravasation as a complication and potential pitfall during hysterosalpingography: Re-emerging study with a novel classification. *J Clin Imaging Sci* 2013;3:67
30. Sonigo C, Robin G, Boitrelle F, et al. First-line management of infertile couple. Guidelines for clinical practice of the French College of Obstetricians and Gynecologists 2022. *Gynecol Obstet Fertil Senol*. 2024;52:305-335.

31. Ludwin A, Ludwin I, Szczeklik W, Martins WP. Cutaneous small-vessel vasculitis following hysterosalpingo-foam sonography (HyFoSy). *Ultrasound Obstet Gynecol.* 2019;54:831-834.

Figures



Figure 1. A case of agent intravasation using ExEm™ foam. The agent is visible within the myometrium (star) and diffusing through uterine radial venous vessels (arrows).

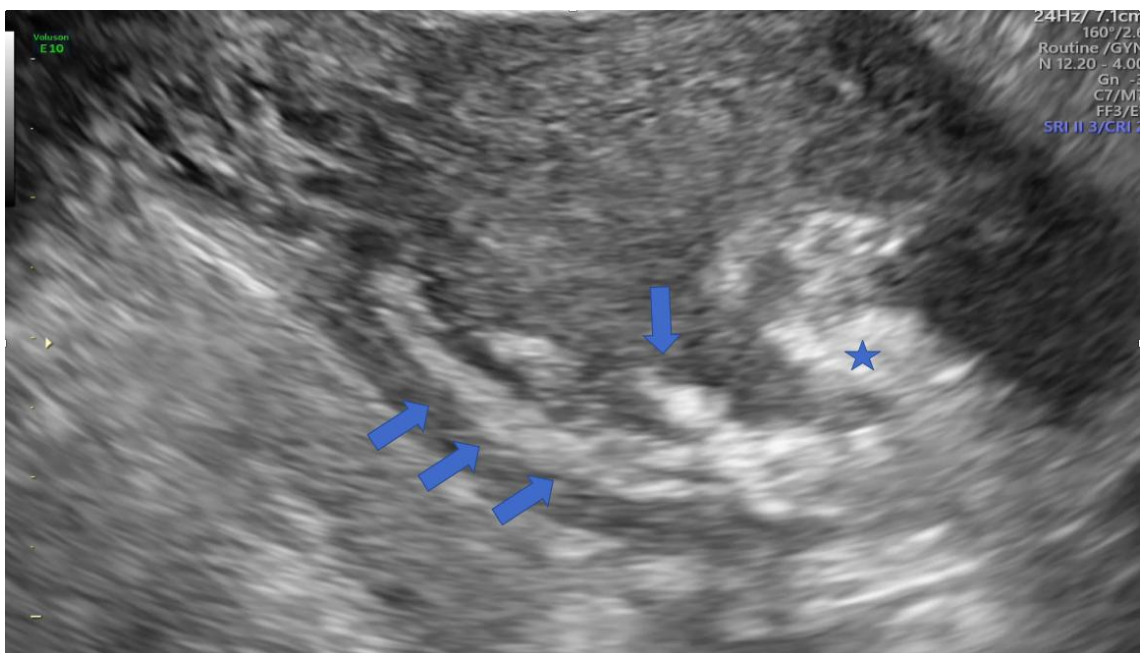


Figure 2. Another case of agent intravasation using ExEm™ foam. The agent is visible within the myometrium (star) and diffusing through uterine arcuate venous vessels (arrows).

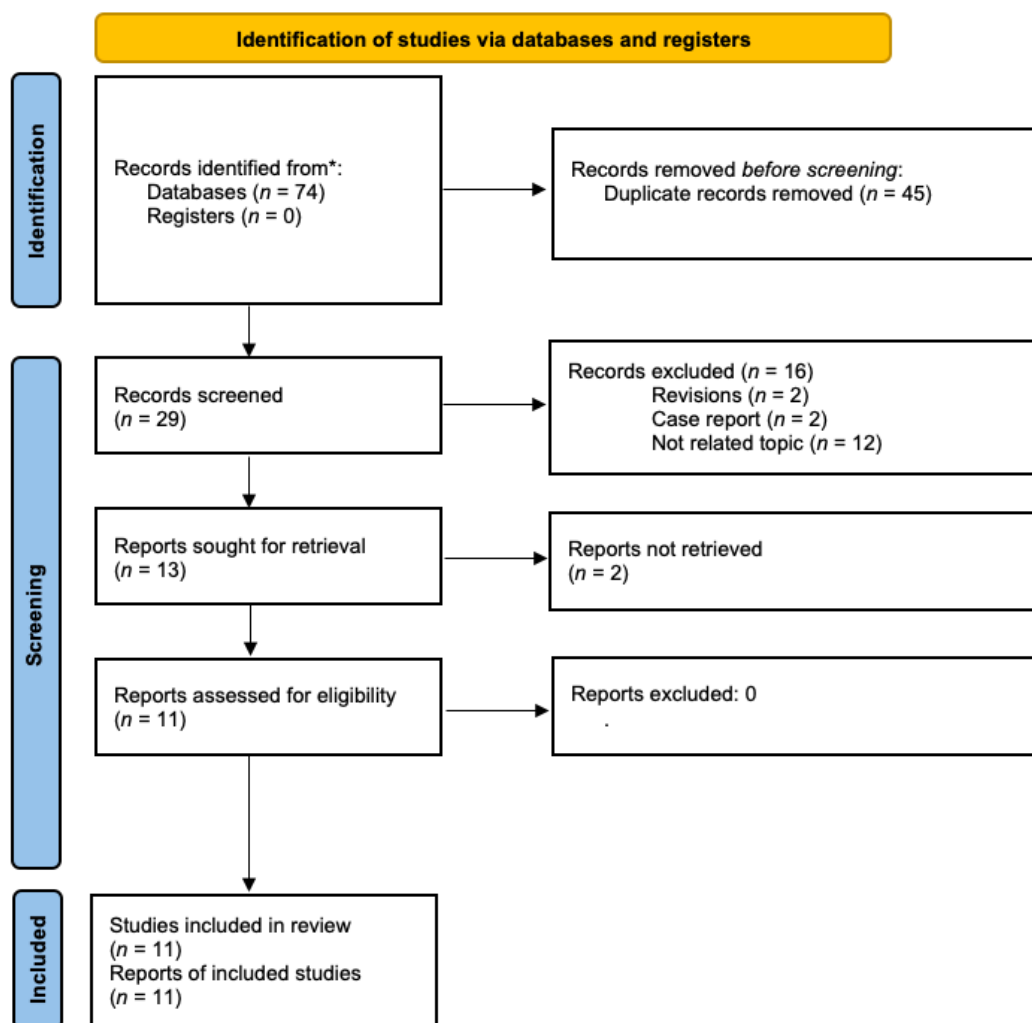


Figure 3. Flow diagram showing search and selection.

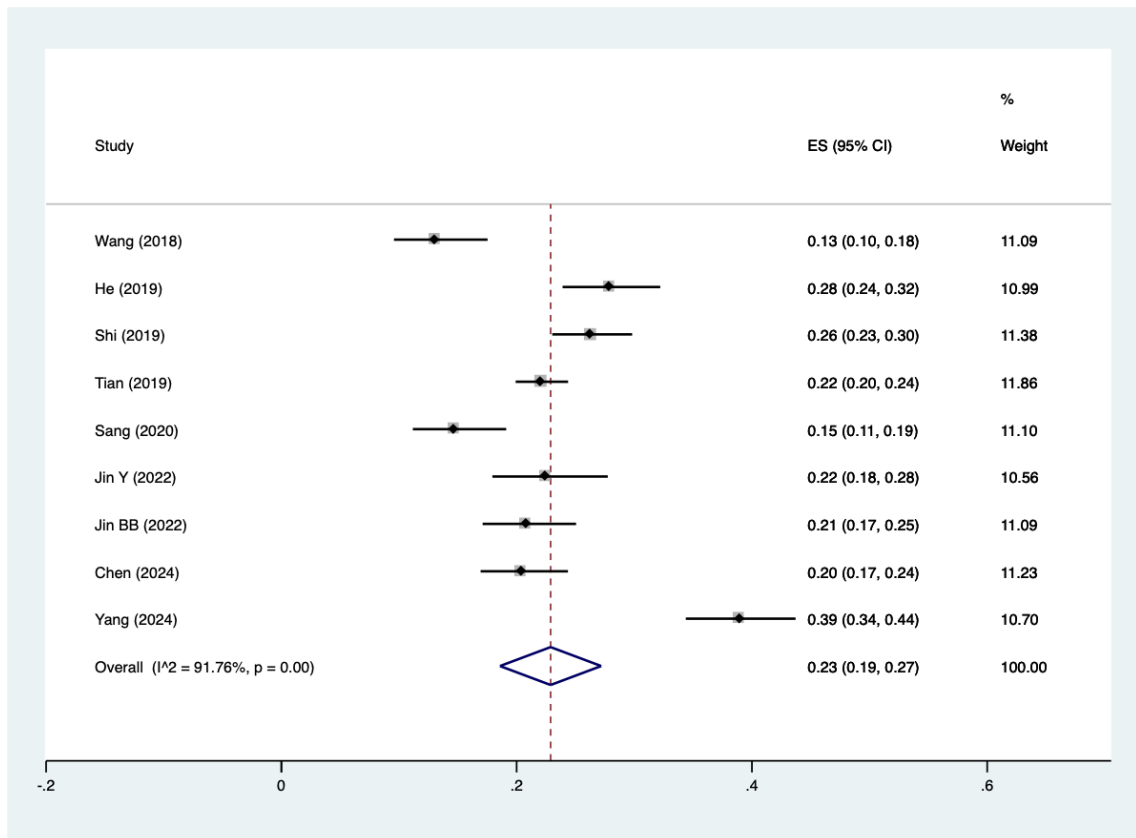


Figure 4. Forest plot of studies using SonoVue™ as contrast agents and the frequency of intravasation observed. Pooled frequency is 23%.

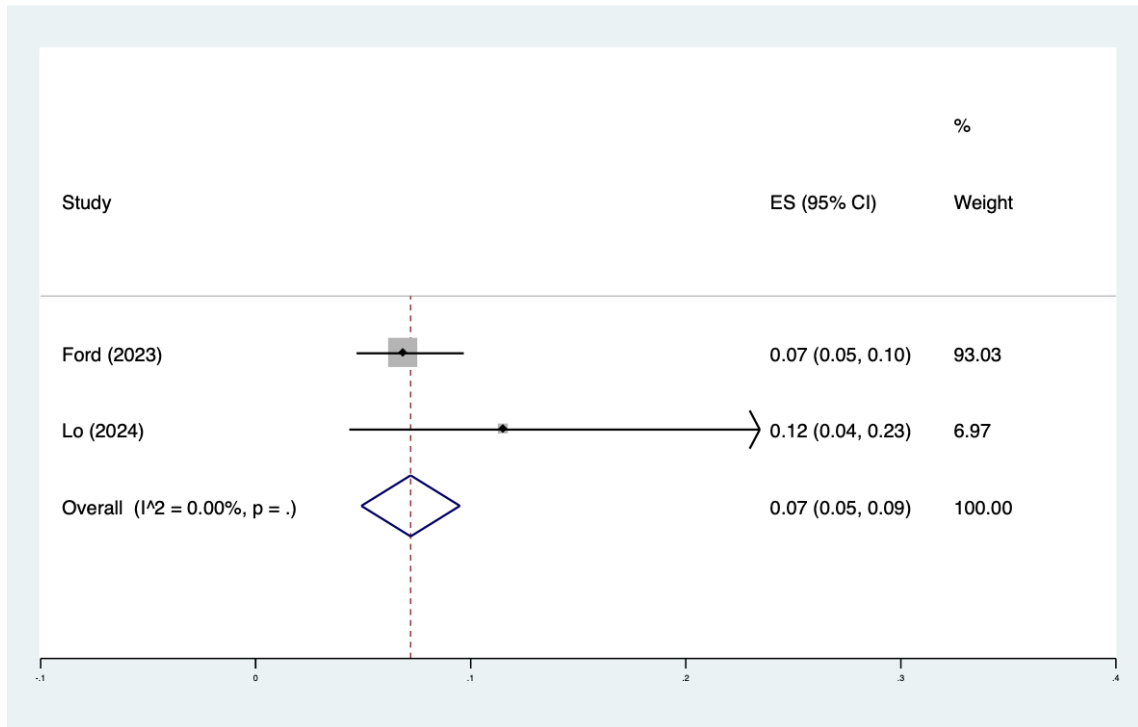


Figure 5. Forest plot of studies using ExEm™ foam as contrast agents and the frequency of intravasation observed. Pooled frequency is 7%. No heterogeneity was observed (I^2 : 0%)