

ORIGINAL RESEARCH ARTICLE

Initial results of magnetic resonance hysterosalpingography diagnostic performance

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ABSTRACT

Objective: to determine the diagnostic performance of magnetic resonance hysterosalpingography (HSG-MRI), using laparoscopy as the reference method. **Materials and methods:** 22 patients were included. All underwent HSG-MRI with a 1.5 Tesla resonator and then laparoscopy with chromotubation. Two radiologists examined the MRIs, determining tubal patency by consensus. Descriptive and diagnostic performance analyses were performed. **Results:** HSG-MRI had a success rate of 91%. Study duration was 49 ± 15 minutes, volume injected 26 ± 16 cm³ and pain scale 30 ± 19 out of 100. Sensitivity and specificity of HSG-MRI were 100% for global and left Cotte test, and 25% and 93.3% for right Cotte test, respectively. There were 2 minor complications and no major complications. **Discussion:** our initial results demonstrated high sensitivity and specificity. Although other studies analyzed the ability of HSG-MRI to assess tubal patency with good results, the use of a flawed reference standard left room for reasonable doubt, preventing a recommendation based on solid evidence. However, when comparing our results with those published, we observed a high degree of concordance insofar as the positive effusion is correctly diagnosed with a specificity of 100% or with a percentage close to this figure.

Keywords: Hysterosalpingography; Infertility; Laparoscopy; Tubal Obstruction; Magnetic Resonance Imaging

ARTICLE INFO

Received: 1 June 2022
Accepted: 24 July 2022
Available online: 29 July 2022

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1. Introduction

Between 10 and 15% of couples have problems conceiving. Of this population, 40–50% of the causes are secondary to the female reproductive system: 20–25% due to the peritoneum, 2–5% due to the uterus and 10% due to the fallopian tubes as an individual cause, and 25–40% as a concomitant cause^[1,2].

Although magnetic resonance imaging (MRI) detects most of these pathologies, no irrefutable tests have yet been provided to determine its real capacity for the evaluation of tubal patency^[2-5]. The most widely used method for this pathology is hysterosalpingography, although it is far from reliable, with a sensitivity of 53–65% and a specificity of approximately 80–87%^[6,7]. Chromotubation (the current reference method) requires a surgical procedure and general anesthesia.

Although hysterosalpingography (HSG) remains the method of

choice for assessing tubal patency and uterine cavity, there is a growing body of published work on the ability of MRI to perform this assessment with dilute gadolinium (Gd)^[1,8-15]. The main weakness of the available literature is the lack of an adequate homogeneous reference method to compare with MRI findings and to understand the real diagnostic capability of MR hysterosalpingography (HSG-MR), since most publications have compared with HSG alone or with a mixture of HSG and occasional laparoscopy^[8,10-15].

If HSG-MRI proved to be reliable in the diagnosis of tubal patency, the target population would have a relatively large number of potential benefits. Patients under study for fertility problems could be provided with a single test to evaluate all diseases: endometriosis, uterine/vaginal malformations, leiomyomas, adenomyosis and polycystic ovarian disease, among others. Given the population, another advantage would be the absence of ionizing radiation, the use of a more innocuous contrast (gadolinium vs. iodine) and the non-requirement of general anesthesia.

In the present study we set out to determine the diagnostic performance of HSG-MRI, using laparoscopy with chromotubation as the reference method.

2. Materials and methods

Approval for this prospective research study was obtained from the Ethics Committee for Research Studies of our institution. All patients included gave informed consent.

2.1 Population

In this ongoing protocol, patients from the Fertility section of the Gynecology service of our institution were prospectively included from July 2010 to May 2014.

The main inclusion criteria for this protocol were patients of childbearing age, referred for diagnostic MRI of the pelvis, with subsequent laparoscopic surgery as the usual treatment.

Exclusion criteria were: active pelvic infection, any type of gynecologic cancer, inability to undergo MRI, pregnancy, history of Gd allergy, and any gynecologic procedure performed between the two

diagnostic methods.

2.2 Magnetic resonance imaging

The MRI was performed in a 1.5 Tesla resonator (Siemens Avanto[®], Erlangen, Germany). The patients were asked to come to the radiology department at least one hour before the study. Upon arrival, they were taken to a private office, where they changed and removed all metallic objects. The patient then had to lie down on a bed and, using a sterile technique, a 5 or 7 Fr hysterosalpingography catheter (Angiotech[™], PBN Medicals, Denmark) was introduced into the uterus with the aid of a speculum. After uterine cannulation, the patient remained on the gurney until the resonator was available. The transfer from the stretcher to the exploratory table of the resonator was performed with sheets, while the patient remained immobile to avoid displacement of the catheter.

Once the patient was positioned in the resonator, the catheter was connected to an automatic infusion pump (Optistar Elite Injector[™], Mallinckrodt, Dublin, Ireland) containing 60 ml of Gd diluted in physiological solution (1:100). A surface body coil was placed over the pelvis and the patient was positioned for pelvic MRI. The routine examination protocol is detailed in **Table 1**.

Dynamic imaging in the intrauterine contrast phase was performed before (VIBE [volumetric interpolated breath-hold examination] and three-dimensional [3D] T1-weighted angiographic sequence), during (True-FISP [true fast imaging with steady state precession] and 3D T1-weighted angiographic sequence) and after intrauterine injection (VIBE and 3D T1-weighted angiographic sequence).

The diluted mixture was injected at a rate of 0.3 ml per second with automatic stop if the pressure exceeded 30 mmHg inside the uterine cavity. The initial injection volume was 20 ml for all patients.

This was reduced if the patient triggered a pain alarm or extended if the console physician performing the procedure considered it insufficient for a diagnostic study.

At the end of the procedure, written instructions and contact numbers in case of complications

were given in all cases. They were also asked to mark on a visual analog pain scale the degree of pain/discomfort felt during the study. No antibiotics were prescribed before or after the procedure.

Three days after the examination, the patients were called to ask them about possible complications and acceptability of the examination.

Table 1. Magnetic resonance examination

Study phase sequence		Orientation of the plane	Angulation	Time of repetition (ms)	Time of exposure (ms)	Field of vision (mm)	Thickness (mm)
No contrast	T1-weighted fat-suppressed turbo spin echo	Axial	-15 °	638	8.8	230	
	T2-weighted turbo spin echo	Axial	-15 °	5,120		230	
	T2-weighted turbo spin echo	Coronal	0 °	4,400		230	
	T2-weighted turbo spin echo	Sagittal	0 °	4,200		230	
	Three-dimensional fluid attenuated inversion recovery	Axial	0 °	6,600	423	254	1.87
Intrauterine contrast	Volumetric Interpolated Gradient Echo (VIBE)	Axial	-15 °	5.91	2.74		2.5
	True-FIST	Oriented to the uterus	Variable	198.1	1.37		3.5
	T1-weighted 3D time-resolved angiographic sequences	Coronal to uterine cavity	Variable	3.42	1.27	320	0.7
Contrast intravenous	T1-weighted fat-suppressed turbo spin echo	Axial	-15 °	638	8.8	230	
	T1-weighted fat-suppressed turbo spin echo	Sagittal	0 °	638	8.8	230	

2.3 Image analysis

The evaluation of tubal patency was performed independently by two radiologists with 8 and 6 years of experience in gynecologic radiology, using the RAIM Alma® software (Alma IT Systems, Barcelona, Spain). All relevant clinical information on the fallopian tubes (hysterosalpingography, surgical resection, etc.) was withheld from the evaluators. In addition, other imaging findings (endometriosis, uterine morphology, ovarian pathology, etc.) were tabulated.

Uterine enlargement was determined by subjective assessment. When there was discrepancy between the findings of the evaluators, agreement was reached by joint interpretation of the images.

2.4 Laparoscopy with chromotubation

The patients underwent surgery no later than three months after the MRI. Chromotubation was performed according to surgical technique before the main surgery. The gynecologist was unaware of the results of the HSG-MRI.

With the patient under general anesthesia, and after insertion of the trocars and the laparoscopic camera, the disposable uterine manipulator, VCare

(ConMed, Utica, New York) was placed. Through the device, 10–20 ml of methylene blue was injected into the uterine cavity to confirm spillage of the dye into the pelvic cavity and thus check tubal patency (**Figure 1**). The data were tabulated.

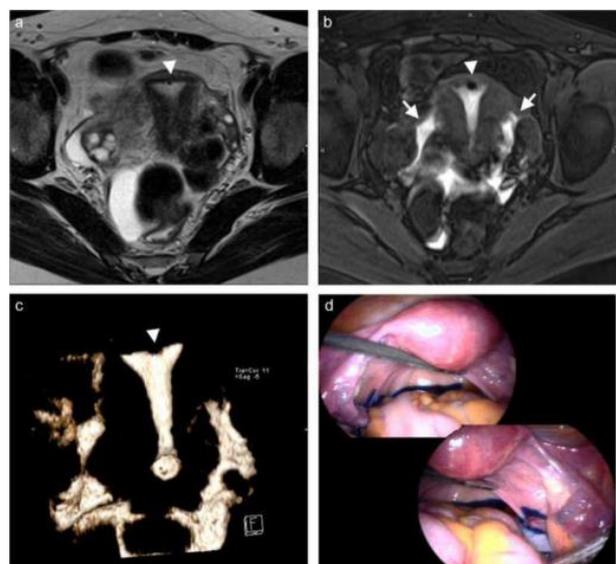


Figure 1. An axial (a) T2-weighted and (b) T1-weighted image with fat saturation post intrauterine injection and (c) a 3D volumetric reconstruction of a successful HSG-MR with bilateral contrast spillage post gadolinium injection (arrows in b), clearly visible in the volume reconstruction. As in conventional HSG, HSG-MR is not free of air bubble formation (arrowheads), but in the latter method the bubbles are easily identified. (d) Confirmation of bilateral tubal patency with chromotubation is shown.

According to chromotubation: 1/19 had bilat-

eral tubal obstruction, 1/19 had left unilateral tubal obstruction and 3/19 developed right unilateral tubal obstruction.

2.5 Data analysis

Continuous variables were described as mean and standard deviation or median and interquartile range, according to the observed distribution; while categorical variables were detailed with proportions. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), precision and likelihood ratio were estimated for the global Cotte test, considered positive for the presence of contrast in the peritoneum and negative for its absence. For the individual Cotte test, each fallopian tube was identified as patent or obstructed. All estimates were calculated with a 95% confidence in-

terval (CI).

Pain or discomfort during the study, measured by visual analog scale, were analyzed with the Mann-Whitney U test for paired samples, using the SPSS 20.0 program (IBM Corp, Armonk, New York). The results were considered statistically significant at a value of $p < 0.05$.

3. Results

Of the 42 patients who agreed to participate and gave consent, only 22 had undergone MRI and laparoscopy at the time of writing (eligibility conditions for this interim analysis). The mean and standard deviation for age, duration of examination, volume injected, and degree of pain are summarized in **Table 2**.

Table 2. Population data and comparison between enlarged uterus and non-enlarged uterus

	Global	Enhanced	Not increased	Mann-Whitney Augmented vs. non-augmented
Age (years)	35 (4)	33.38 (3.6)	37.57 (4.4)	
Duration of study (min)	49 (15)	52 (17.5)	44 (8.6)	0.338
Volume injected (ml)	26 (16)	35.29 (21.5)	18.7 (3)	0.026
Intrauterine pressure (psi)	10 (9)	14 (14)	8.6 (3.6)	0.742
Pain scale	30 (19)	20.86 (15.9)	36.54 (17.8)	0.145

Values are expressed as mean (standard deviation).

Table 3. Sensitivity and specificity of magnetic resonance hysterosalpingography

	Sensitivity	95% confidence interval	Specificity	95% confidence interval
Global Cotte	100	2–100	100	94.5–100
Cotte left	100	51–100	100	94.2–100
Cotte right	25	0–91.9	93.3	74.2–100

Table 4. Concordance between magnetic resonance hysterosalpingography and chromotubation

	Concordance
Uterine morphology (normal vs. altered)	100%
Type of morphology	100%
Uterus size	86%
Myomas (presence vs. absence)	95%
Number of fibroids* Number of fibroids	31%
Adenomyosis* (presence vs. absence)	95%
Hydrosalpinx (presence vs. absence)	91%
Adherences† (presence vs. absence)	50%
Endometriosis (presence vs. absence)	82%
Non endometriotic ovarian pathology (presence vs. absence)	91%

* MRI showed more pathology than surgery

† Chromotubation showed more pathology than MRI.

Of the 22 cases, 2 HSG-MR and 1 chromotubation could not be performed, so the success rate was 91% for HSG-MR and 95% for chromotubation. The inability to perform HSG-MR was due to catheter displacement due to compliant cervical orifices, while the failure of chromotubation was due to the need to convert the surgery to a laparotomy.

The volume injected was significantly different between patients with an enlarged uterus due to leiomyomas and those with a normal-sized uterus (**Figure 2, Table 2**). Scan time and pain did not vary significantly.

The overall and individual sensitivity and specificity data for HSG-MRI are shown in **Table 3** and the agreement between HSG-MRI and laparoscopy is shown in **Table 4**.

There were 2 minor complications (clinically irrelevant bleeding) in the 22 cases at 72 hours of follow-up and no major complications. The patients referred to the bleeding as spotting that lasted for the first 24 hours and disappeared spontaneously after that time.

Acceptance of the method was high: 91% reported that they would “certainly” (77%) or “very probably” (14%) repeat the study. In women who

had previously undergone hysterosalpingography, the percentage was 86% (6/7).

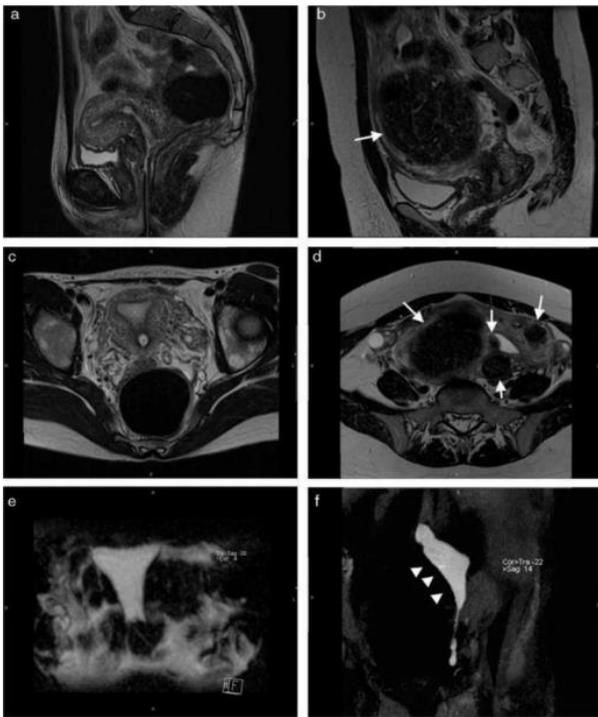


Figure 2. Sagittal and axial T2-weighted images and maximum intensity projection (MIP); reconstruction of (a, c and e) a normal uterus and (b, d and f) an enlarged uterus. The leiomyomas (arrows in b and d) are clearly identified on MRI and increase the size of the uterus and the uterine cavity, which appears deformed on the MIP image, as the outline of the dominant leiomyoma is observed (arrowheads). Enlarged uteri required more contrast injection than normal sized uteri in order to perform HSG-MR in our study group.

4. Discussion

Our initial results on the diagnostic performance of HSG-MRI for the evaluation of tubal patency have demonstrated high sensitivity and specificity compared to the true gold standard method for this evaluation, laparoscopy with chromotubation (Figures 1 and 3). Even when each fallopian tube was considered separately, and despite not being able to visualize in some patients the very contour of the tube, a high sensitivity and specificity was observed for the left tube and a high specificity for the right tube. The cause of the low sensitivity observed in the latter is still unknown and warrants further investigations with a larger population sample.

Although other studies have looked at the ability of MR-HSG to assess tubal patency and have already yielded good results, the use of a flawed

reference standard, such as conventional HSG, left room for reasonable doubt as to its true ability, so that a recommendation based on solid evidence could not be made^[1,8,10-15]. Nevertheless, comparison of our results with those published (comparing MR-HSG with conventional HSG alone or a combination of conventional HSG and laparoscopy) identifies a high degree of agreement in that positive effusion is correctly diagnosed with a specificity of 100% or close to this percentage^[11-13].

Comparison of our results on tubal obstruction with those of the other authors could not be made because in those studies HSG-MRI was not the initial study or laparoscopy was not performed in patients with unilateral obstruction^[11,12,15]. Likewise, some authors detected more patent tubes with MR-HSG than with conventional HSG, which was attributed to greater tissue contrast or to a secondary result of the initial procedure^[11,12]. We could also assume that in the cases in our study in which HSG-MRI showed unilateral obstruction (n = 3) and laparoscopy showed patency, removal of the obstruction could have been achieved by HSG-MRI, but more studies and a larger number of patients are required to support this assumption.

In addition to allowing visualization of tubal patency without iodine or radiation, HSG-MRI helped to detect previously unknown diseases in the study population, as previous studies have reported^[11]. Specifically in our case, up to 23% of patients were found to have a condition that they did not know they had (reinforcing the potential ability of this procedure to become the only test required for patients with fertility problems). Also, most of the findings reported on HSG-MRI correlated with those reported at surgery. A low correlation of HSG-MRI with surgery was only found in the case of peritoneal adhesions, since thin adhesions could not be detected by MRI sequences, resulting in an underestimation of pelvic endometriosis.

Although gadolinium is not currently marketed for intrauterine use, many reports have demonstrated its safe use as an iodine substitute in allergic patients on conventional HSG and HSG-MRI, and it has also been shown in animals not to affect reproductive function^[1,8,10-14,16-19].

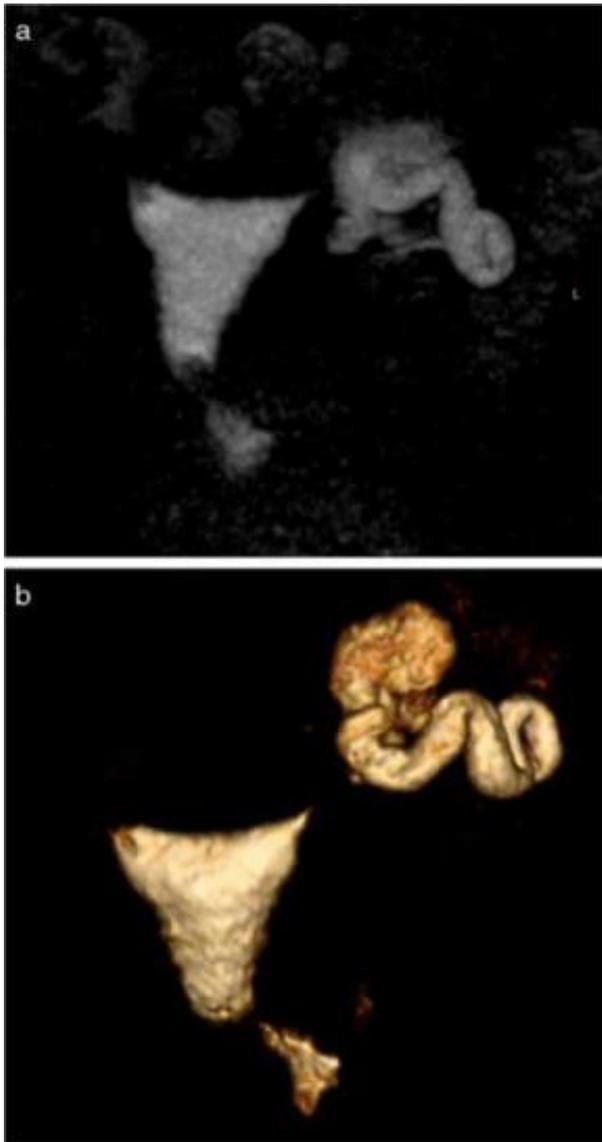


Figure 3. (a) Maximum intensity projection reconstruction and (b) volumetric reconstruction in a 29-year-old female patient with a history of endometriosis and right adnexectomy. The lack of gadolinium passage to the right fallopian tube is consistent with her medical history. There was also a lack of contrast leakage from the left fallopian tube, which was slightly dilated. Chromotubation confirmed the finding.

In our study, gadolinium was used in a 1:100 dilution, as in other publications, since at this concentration it has diagnostic capability^[11,12]. It should be noted that this dilution is significantly lower than when gadolinium is used as a substitute for iodine (in which case no dilution is performed due to the lower density of Gd)^[17,18]. The mean volume used in our study was 26 ml, although larger volumes (mean: 35.29 ml) were required for enlarged uteri. This should be taken into account when testing myomatous or enlarged uteri due to other pathologies (e.g., adenomyosis).

With respect to study duration, the mean in our case was longer than that of other published studies^[8]. However, our examination protocol included routine pelvic MRI which accounted for 80% or more of the MRI examination. We assume that once HSG-MRI is introduced into our clinical routine, a rapid examination proto-collage with three-plane T2-weighted spin-echo turbo echo in three planes and the sequences used for tubal patency will suffice to evaluate 90% of patients in examinations of no more than 15 minutes duration. Those cases requiring a more detailed study could complete the HSG-MRI with a complete pelvic MRI protocol and intravenous injection of Gd on a subsequent day.

In turn, in our study group, the 3D sequence with flow-attenuated inversion recovery (FLAIR), of approximately 4 minutes, was part of the examination protocol in order to evaluate the data of Rouanet De Lavit *et al.*^[20] on better visualization of endometrial tissue using this sequence, so this also influenced our study times. Nevertheless, no patient interrupted the examination because of the prolonged duration of the exam.

Pain was assessed with a visual analog scale. This showed a high tolerability (mean 30/100) and correlated well with previously published work, although none of them had assessed pain so objectively^[13,14]. The acceptance rate of the procedure, measured by a telephone questionnaire asking whether they would repeat the study in the future, is also in line with previously published literature of De Felice *et al.*^[8].

The main weakness of this work is the small population. This does not allow us to conclude with certainty that the sensitivity and specificity of HSG-MRI are those demonstrated by our results. Also, the small number of patients and the absence of false positives and false negatives in the estimation of the sensitivity of the global and left Cotte test results in a large confidence interval. This value is expected to be similar to that reported for conventional HSG if more false positives and false negatives begin to appear in patients in the future in this ongoing study. However, no other publication on HSG-MR has compared all its patients with chromotubation, which is the currently accepted

reference method for tubal patency and the one used to evaluate conventional HSG at the time^[6].

Another weakness to mention in this study is that only a 1.5 T resonator was used. This means that, although no worse is expected, our results may not be a reliable predictor of the diagnostic performance of HSG-MRI performed with 3 T resonators.

Finally, although a dynamic sequence was used to assess the correct filling of the uterus with gadolinium, we lack the great dynamic assessment provided by fluoroscopy during conventional HSG with an overview and clear contrast advancement through each fallopian tube. Nevertheless, we have observed that individual evaluation of each fallopian tube is not impossible without such information. It is expected that with the evolution of sequences and MRI technology an appropriate sequence to visualize and evaluate the progression of contrast through the fallopian tubes will emerge.

5. Conclusion

HSG-MRI has proven in our study to be a feasible and safe alternative to conventional or virtual HSG, hysterosonography and chromotubation. It has high overall sensitivity and specificity for the detection of tubal patency, a high success rate and high patient acceptance, while being able to evaluate the female pelvis for other concomitant diseases affecting fertility.

Conflict of interest

The authors declare that they have no conflict of interest.

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