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Comparison of Hystero-salpingography and Hysterosalpingo-Contrast Sonography for tubal patency testing: technical success, pain perception, side effects and complications

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Abstract

Aims: The aim of this study was to compare technical success and tolerability between hysterosalpingography (HSG) and hysterosalpingo-contrast ultrasonography (HyCoUs) as a first-line evaluation method in a single fertility center. **Material and methods:** The study included 56 infertile women: 27 patients underwent HSG and 29 patients underwent HyCoUs. Pain perception was measured by means of an 11-point visual analog scale (VAS) and the Stacy score. Side-effects, technical aspects, complications and variable correlations were documented. **Results:** The median VAS scale was 5 (4;6) for HSG and 1 (1;2) for HyCoUs. The median Stacy score was 2 (1;3) for HSG and 1 (0;1) for HyCoUs. The difference in pain perception was statistically significant for both pain scores ($p<0.001$). All patients undergoing HyCoUs reported a visual analog (VAS) pain score of <5 and 59.3% of patients undergoing an HSG reported a score of >5. Increased pain scores showed a statistically significant association with duration and total volume of substance infused. The type of procedure and volume infused were independently associated with the VAS scale. In the HSG group, 14.8% (4) of patients reported a vagal effect ($p<0.001$), one patient requiring hospitalization. No vagal effects were reported following HyCoUs and the method was technically successful in 100% (29) of cases. HSG was successful in 88.9% (24) of cases. Conclusions: HyCoUs is a well-tolerated procedure with reduced frequency of adverse effects. Low pain perception is strongly correlated with a low volume infused. It is non-invasive and efficient in rendering good quality images.

Keywords: Hysterosalpingography; tubal obstruction; pain perception; infertility; hysterosalpingo-contrast ultrasonography

Introduction

The initial infertility workup requires reproducible, diagnostically accurate, minimally invasive and cost-effective approach. The first evaluation plays a major role in the future recommendations for assisted reproduction techniques such as intrauterine insemination or in vitro fertilization. Out of the couples addressing a fertility center, 14% require treatment for uterine or tubal pathology [1]. For this reason, assessment of tubal patency and normal uterine cavity is the first-step examination in the morphological evaluation of infertile women.

Assessing the anatomy of the female reproductive organs involves complex diagnostic modalities, some of them being invasive, adding up to significant psychological distress in a particularly burdening patient situation. Currently, laparoscopy with chromopertubation is considered the gold standard test for tubal assessment, completed by hysteroscopic examination of the uterus. This approach, however, is not feasible as the first line evaluation due to high costs and potential surgical complications [2,3].

In some fertility centers, radiologic hysterosalpingography (HSG) is the method of choice for tubal and uterine

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patency evaluation, even though it has some clear limitations such as atopic phenomena triggered by the contrast agents used, no real time examination of the pelvic organs and the use of ionizing radiation [4].

Ultrasound (US) is an increasingly preferred imaging technique for infertility evaluation in women [5]. Two-dimensional (2D) vaginal US is the first tool used for investigating the uterus, adnexa and ovaries. It can be performed in an outpatient setting, during the initial consultation [6]. Acquisition of a three-dimensional (3D) volume offers a complete examination of the shape of the uterus and ovarian follicle count [7].

Hysterosalpingo-contrast ultrasonography (HyCoUs) is an US examination of the uterus and Fallopian tubes which allows the assessment of tubal patency by means of a transcervical contrast agent (air-saline or micro bubble contrast agents) [8,9]. Several studies have shown that HyCoUs displays high specificity and sensitivity for tubal and uterine cavity assessment [10-16]. On the other hand, there is a high variation in protocols (timing, duration, contrast medium, volume infused) and limited evidence on patient tolerability and actual complications rates [17,18].

For this reason, the aim of this prospective study was to compare technical success and tolerability between HSG and HyCoUs.

Material and methods

A prospective, interventional, analytical, case-control study, including 56 patients from the Polisano Fertility Center, Sibiu, Romania was conducted between January 2018 and May 2019. The institutional Ethics Committee approved the study and all participants signed an informed consent form.

Inclusion criteria were: female patients aged between 18-40 years with a history of infertility, previously uninvestigated for uterine or tubal anomalies, presenting to the fertility center for an initial diagnostic work-up. All patients were required to have a normal cervical cytology within the last 6 months and negative bacteriology testing from the cervix in the last 3 months. Exclusion criteria were history of infertility of less than one-year, abnormal vaginal bleeding, acute pelvic infections and genital malignancies. In figure 1 the selection process of the patients is detailed. A total of 56 patients were randomized by means of a sealed envelope system. Women in both groups did not receive any pain medication before undergoing the procedure and no antibiotic therapy was prescribed. Verbal anesthesia was used in all cases, with extensive patient counseling before all procedures, including visual aids explaining the examinations in detail [19].

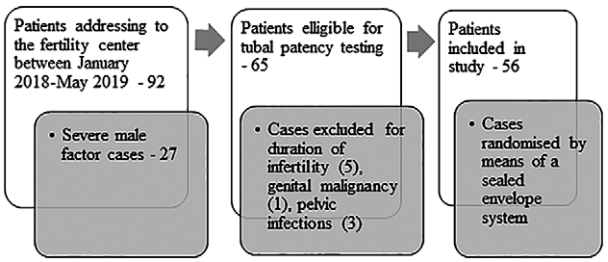

Fig 1. Flow chart with selection process of the patients

All procedures, both HSG and HyCoUs, were performed by the same practitioner, an obstetrics-gynecology specialist with more than 5 years of experience.

HSGs were performed at the institution's radiology unit within the first 12 days of the menstrual cycle. The HSG was performed as follows: the cervix was exposed with a speculum and, after local disinfection, a Pozzi cervical tenaculum was applied. After attaching a Schulze salpingogram cannula, the speculum was removed and the ioversol solution (Optiray 350, 741mg/ml, Guerbet) slowly injected under radioscopic guidance. A total of 2 radiographic images were taken - first after injecting 5-10 ml of contrast to check for uterine cavity and correct positioning of the cannula and the second 20 minutes after the beginning of the procedure to check for passage of the contrast medium through the Fallopian tubes into the peritoneum. After injecting the contrast medium and obtaining a satisfactory image of the uterus and tubes, the tenaculum and canula were removed for patient comfort until the last radiographic image was acquired. The duration of each procedure and the volume of contrast needed in each case to acquire good quality images were also documented.

The HyCoUs examinations were performed using a Samsung WS80A machine with 2D/3D/4D/contrast enhanced US (CEUS) software and endocavity transvaginal transducer. Routine 2D transvaginal examination of the uterus, endometrium, ovaries and Douglas pouch was initially done, scanning for any morphological abnormalities and also localizing the interstitial part of the salpinges before injecting the contrast medium followed by a 3D volume acquisition of the uterus (fig 2).

Then, the cervix was exposed with a single-use vaginal speculum, disinfected with ethanol and a single-use Labotect 3-way balloon catheter was introduced inside the uterine cavity through the cervical os. The catheter was fixed inside the uterus by filling the balloon with 2 ml of air and then the vaginal speculum was removed. The CEUS examination was performed using SonoVue, (Bracco, Milan Italy) undiluted contrast medium: 5 ml of substance was slowly injected through the catheter while performing a full transvaginal scan of the uterine cavity

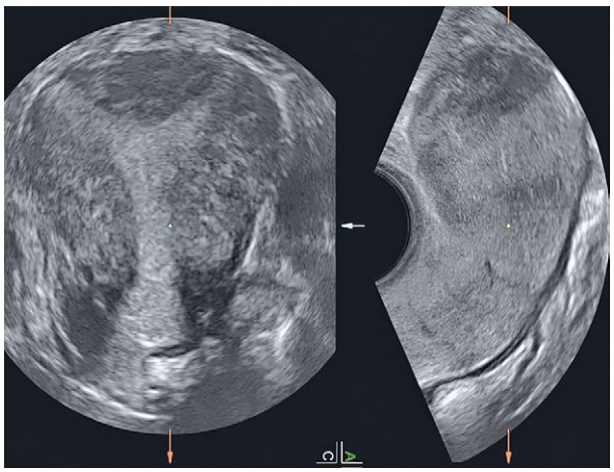

Fig 2. Transvaginal 3D ultrasonography volume acquisition of the uterine cavity

and tubes (fig 3). At the end of the procedure, the balloon was deflated and the catheter removed.

Immediately after either procedure, the patients were questioned about the pain experienced using an 11-point visual analog numerical rating scale (VAS) where 0 represents no pain at all and 10 severe pain. The pain caused by the procedures in comparison to menstrual pain was also assessed (Stacy score) where 0 was no reaction or discomfort, 1 - slight pain less than menstrual pain, 2 - moderate pain, exceeding menstrual cramps but no vagal effects, 3 - vagal effects or pain requiring hospital observation, 4 - vagal effects or pain requiring resuscitation [20]. The vagal effects consisted of nausea and/or vomiting, dizziness, syncope, hypotension and bradycardia.

The frequency of difficult examinations was documented in both groups, such as impossible catheter passage or lack of satisfactory visualization of the uterus and/or Fallopian tubes, resulting in rates of technical success for each respective examination method.

Statistical analysis

Statistical analysis was carried out using the MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). Median and 25-75 percentiles were used to describe the quantitative variables and frequencies and percentages for nominal variables. Between-group comparisons were performed using the Man-Whitney test for quantitative variables and the chi-square tests or Fisher's exact test, for nominal variables. Spearman's rho was used to test the correlation between quantitative variables. A multiple linear regression was used in order to find out which variables were independently associated with the pain score. VAS scale values were logarithmically transformed in order to normalize the distribution. Variables that achieved a $p<0.2$ in the univariate analysis, were introduced in the multivariate analysis. A p value <0.05 was considered statistically significant.

Results

The 56 patients were randomized by means of a sealed envelope system: 29 underwent a HyCoUs (group 1) and 27 underwent HSG (group 2). There was no significant difference between the two groups concerning the age, infertility duration or the days of menstrual cycle when the procedure was performed. The pain appreciated on VAS and Stacy score and the volume infused were higher in the second group but the duration of the procedure was longer in the first group (all $p<0.001$) (Table I).

No significant technical difficulties or incidents occurred during the HyCoUs. HSG vagal effects were reported in 14.8% of cases ($p<0.001$). The detection frequency for unilateral or bilateral salpinges obstruction has no significant differences between the two groups ($p>0.05$) (Table II).

Tables III and IV show the association between several variables and the reported pain intensity on VAS scale. Statistically significant correlations were found between VAS and duration of procedure or infused volume. Patients with vagal effects experience significantly worse pain.

In order to find out which variables were independently associated with the pain we used the multiple lin-

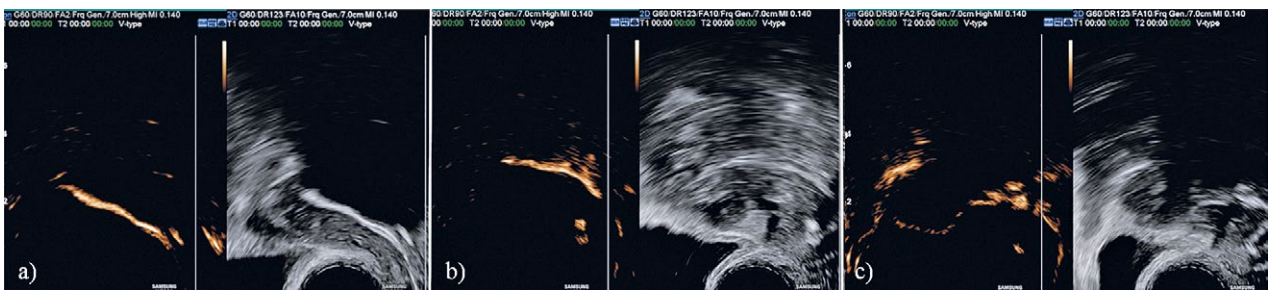

Fig 3. Transvaginal contrast enhanced ultrasonography: a) sagittal view of the uterine cavity; b) view of the Fallopian tube with contrast passage; c) view of the periovarian spill of contrast after tubal passage

Table I. Clinical features, procedure timing, mean pain scores and technical aspects

Variable	HyCoUs (n=29)	HSG (n=27)	P
Age (years)	31 (27.5;35)	34 (30;36)	0.1
Duration of infertility (years)	3 (2;5)	3 (2;5)	0.9
Days of menstrual cycle	9 (8;10)	9 (8;10)	0.5
Visual analog pain score	1 (1;2)	5 (4;6)	<0.001
Stacy score	1 (0;1)	2 (1;3)	<0.001
Duration of procedure (minutes)	20 (15;22.5)	10 (10;10)	<0.001
Volumes infused (mL)	5 (5;5)	10 (10;10)	<0.001

The results are expressed as mean (low;high); HyCoUs – hysterosalpingo contrast sonography; HSG – hysterosalpingography; n – number

Table II. Adverse effects, technical difficulties and tubal obstruction in study groups

Variable	HyCoUs (n=29)	HSG (n=27)	P
Vagal effects	0 (0)	4 (14.8)	<0.001
Failed attempt	0 (0)	3 (11.1)	0.1
Unilateral obstruction	3 (10.3)	3 (11.1)	1
Bilateral obstruction	2 (6.9)	5 (18.5)	0.2

The results are expressed as number (%); HyCoUs – hysterosalpingo contrast sonography; HSG – hysterosalpingography; n – number

Table III. Pain score correlations

Variable	VAS*	
	r	P
Age (years)	0.176	0.1
Duration of infertility (years)	0.028	0.8
Days of menstrual cycle	0.162	0.2
Duration of procedure (min)	-0.415	**0.001**
Volume infused (ml)	0.792	**<0.001**

*VAS – visual analog scale

Table IV. VAS association with adverse effects and conditions

Variable		VAS*	P
Vagal effect	Yes	6.5 (3.5; 8.75)	**0.02**
	No	3 (1; 4.75)	
Failed attempt	Yes	5 (3; 5)	0.1
	No	3 (1; 5)	
Unilateral obstruction	Yes	3 (1.75; 5.75)	0.6
	No	3 (1; 5)	
Bilateral obstruction	Yes	4 (2; 5)	0.3
	No	3 (1; 5)	

*VAS – visual analog score

ear regression (table V). The type of the procedure and the volume infused were independently associated with the VAS scale.

Discussion

Few studies have focused on patient compliancy to the ultrasound method in comparison to other investigations such as HSG. The current study focuses on pain perception, technical aspects and complications of the two methods. Our data showed that HyCoUs is a well-tolerated examination with a low rate of complications and side effects. We found statistically significant difference in pain perception by VAS and Stacy score, in favor of HyCoUs. Our results complement the results reported by Savelli et al [21] in a prospective study; the authors reported a mean numeric rating scale of the pain of 2.7±2.5.

Ayada et al compared HyCoUs to conventional HSG regarding the tolerability of the procedure [22]. Sixty-six patients with infertility underwent one of the two procedures and the authors reported no significant difference in procedure time, volume of contrast infused, patient tolerability or adverse effects. We found significant difference in the duration of the procedure between the two techniques, HyCoUs needing longer time. This might be explained in a subjective manner related to the experience of the physician performing the examinations but is also related to the different equipment used.

In the study of Socolov et al, the authors reported a higher pain score for HyCoUs with no correlations between pain intensity on the analog/digital scale and any of the variables analyzed [23]. We, however, found significant correlation between the volumes of contrast infused and pain intensity, as well as a significant inverse relation between the duration of procedure and pain score. In our study, for the HyCoUs procedure, we used maximum 5 mL of SonoVue compared to a maximum of 10 mL of ioversol contrast for HSG, which rendered sufficient information to document tubal patency and uterine cavity morphology with minimum discomfort for the patient. The difference in amount of contrast infused could explain the higher pain score reported by patients in the

Table V. Multiple linear regression for VAS

	Unstandardized coefficients		t	P	95%CI for B*	
	B	Std. Error			Min	Max
(Constant)	-0.113	0.222	-0.509	0.6	-0.559	0.334
HSG	0.358	0.093	3.836	**<0.001**	0.170	0.546
Age	0.000	0.006	0.079	0.9	-0.011	0.012
Duration of procedure (min)	0.008	0.006	1.308	0.1	-0.004	0.020
Volume infused	0.029	0.012	2.447	**0.01**	0.005	0.052
Vagal effect	0.069	0.129	0.534	0.5	-0.191	0.329
Failed attempt	-0.026	0.154	-0.168	0.8	-0.335	0.284

*B – regression coeficient

Socolov et al study. The Sono Vue microbubble contrast agent generates a stronger acoustic signal compared to the air in the saline agent used in the Socolov et al study and could explain the different results. Also, the sealing of the cervical os with the inflated catheter balloon reduces leakage of the substance outside the salpinges and uterus towards the vaginal canal. Using this equipment adds up to a longer duration of the HyCoUs but reduces the volume necessary for performing the examination and results in lower pain scores.

Regarding adverse effects of the two procedures, for HSG we report 4 (14.8%) cases of vagal effects and 3 (11.1%) cases of failed passage attempts. HyCoUs, however, was well toleratedwith no vagal reactions or post-procedural complications. We were able to canulate the uterine cavity in all cases. Hamed et al [24] reported a low global rate of vagal effects (5.7%) and Savelli et al [21] reported a rate of 4.1% mild vagal effects in patients undergoing HyCoUs.

The difference in technical difficulties and complications is possibly related to the different instruments used in our center. The HyCoUs canula that we use is similar to those used in intrauterine insemination procedures and is more malleable. The rigid Schulze canula used in other centers that perform HSG offers less maneuverability, less precision in difficult patients (obese, nulliparas) and more pain when applied [25].

The findings of this study have to be seen in light of some limitations, one of them regarding the instruments used. The two procedures were not performed using the same type of uterine cannula. We attempted to use the flexible HyCoUs canula for HSG as well but this poses a lot of difficulty because HSG does not offer real time positioning of the canula. This leads to inconclusive examinations, repeated manipulation of the cervix and more discomfort for the patient [26]. Another limitation of our study is the sample size, though representative for the studied population, results could benefit from a larger cohort of patients. This would allow for more extensive variable correlations regarding technical difficulties and adverse effects of the two procedures. Also, all of the examinations were performed by the same examiner, an infertility specialist from our center.

A longitudinal approach to the study population could offer valuable data regarding benefits of either examination techniques in obtaining pregnancy. Few studies have focused on rates of spontaneous pregnancy obtained after tubal patency testing as a result of contrast passage through the salpinges.

We consider that extensive counseling patients underwent before the procedures played an important role in reducing pain perception and stress-related discomfort during the examinations. Patients were kept informed about every step of the investigation before and during HSG/HyCoUs and were advised about the nature of the discomfort they might feel. Verbal anesthesia is carried out before and during the procedure and is aimed at establishing a calm and familiar environment for the patient by means of conversation steering their attention away from the uncomfortable moments experienced during the intervention. It is a relaxation technique widely used for in-office minimally invasive procedures and significantly reduces the need for pain medication.

Further studies are required with a larger patient sample size that would enable us to establish a complete in-office examination protocol for pelvic anatomy performed in a single-visit concomitant to the HyCoUs that would be suitable as a first-line evaluation in a fertility center.

In **conclusion**, HyCoUs is a well-tolerated procedure with low rates of adverse effects and low pain perception. Volume of contrast agent infused correlates independently with pain perception. HyCoUs is safe, non-invasive and efficient in rendering good quality images regarding pelvic morphology in infertile patients. Therefore, the technique could be used as a first line evaluation method in an office setting for women undergoing infertility treatment.

Conflict of interest: none

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