A randomized study comparing air to Echovist® as a contrast medium in the assessment of tubal patency in infertile women using transvaginal salpingosonography

H.Spalding1, H.Martikainen, A.Tekay and P.Jouppila

Department of Obstetrics and Gynaecology, University Hospital of OLE, Kajaanintie 50, 90220 Oulu, Finland

1To whom correspondence should be addressed

This study was undertaken to compare two different contrast media (air and Echovist®) in the assessment of tubal patency using transvaginal salpingosonography (TSSG) in 32 infertile women referred to an infertility outpatient clinic. Altogether, 59 Fallopian tubes were examined with TSSG. Laparoscopic chromoperturbation was used as a reference method. In group A (air), concordance was 90%, Cohen's kappa coefficient 0.71 [95% confidence interval (CI): 0.64–0.77], sensitivity 63%, specificity 100%, negative predictive value 88% and positive predictive value 100%. In group B (Echovist®), the corresponding parameters were as follows: 93%, 0.71 (CI: 0.67–0.76), 60, 100, 93 and 100% respectively. No statistically significant differences were found between these two contrast media. Either one can reliably be used for assessing tubal patency with TSSG in infertile women as a primary phase examination modality. Key words: air/Echovist®/transvaginal salpingosonography/ tubal patency

Introduction
Assessing tubal patency is of great importance in the clinical work-up of infertile patients, as ~25–30% of female infertility is due to tubal damage. The result of primary examinations greatly influences the future course of treatment.

Laparoscopic chromoperturbation and X-ray hysterosalpingography (HSG) have previously been the main examination methods for assessing tubal patency. Both methods, however, have a number of inherent limitations and disadvantages: laparoscopy is an invasive and high cost procedure requiring general anaesthesia and hospitalization. The risk of injury to abdominal vessels and bowel is also present with this procedure. The assessment of fimbrial function and the detection of adhesions, on the other hand, is only possible with laparoscopy. HSG is associated with an increased risk of allergic reactions, an exposure to radiation and to pain. Visualization of the ovaries and pelvic lesions is impossible using HSG. As compared to diagnostic laparoscopy, HSG has a sensitivity of only 44% in the detection of proximal tubal obstructions with a specificity of 92% (Mol et al., 1996).

Transvaginal salpingosonography (TSSG) has recently been introduced as an alternative method for assessing tubal patency in infertile women as it is an easily repeatable, well-tolerated, safe and inexpensive procedure. The use of TSSG as a diagnostic tool is limited in that we are still unable to define peritubal adhesions or endometriosis. It does, however, provide a potentially useful initial test of Fallopian tube patency. The accuracy of this method using air or an echogenic contrast medium (Echovist®) has varied in the literature between 85 and 88% (Deichert et al., 1989; Schlieff and Deichert, 1991; Heikkinen et al., 1995; Volpi et al., 1996; Spalding et al., 1997; Tekay et al., 1997). Echovist® is a galactose based solution containing micro-air-bubbles. In many countries the TSSG combined with the use of Echovist® is called hysterosalpingo-contrast sonography (HyCoSy).

As our experiences with air as a contrast medium have been encouraging, we wanted to compare these two different contrast media (air and Echovist®) in assessing tubal patency using laparoscopic chromoperturbation as a reference method in infertile women.

Materials and methods
An unselected group of patients attending the in-vitro fertilization (IVF) unit of our hospital and scheduled for laparoscopic chromoperturbation due to infertility were asked to participate in this study between March and August, 1996. They were randomized into two groups with a computer programme. Altogether 32 patients were included. TSSG was performed using air in 16 patients (group A) and Echovist® (SHU 454, Schering AG, Berlin, Germany) in 16 patients (group B). All salpingographies were performed by the same investigator (H.S.). A laparoscopic chromoperturbation was performed on the same day or the day after TSSG.

All patients were studied in the follicular phase of the menstrual cycle, after the bleeding had ended (i.e. between days 6-12). A normal gynaecological examination was performed before transvaginal sonography and no signs of infection were observed. All patients received orally 2 g of metronidazole (Trikozol®, Medipolar, Oulu, Finland) or tinidazole (Tricani®, Orion, Espoo, Finland) as a prophylactic antibiotic after the procedure.

The women were examined in the dorsal lithotomy position. The patient's vulva and vagina were disinfected using chlorhexidine (Travalox®, Baxte Healthcare Ltd, Norfolk, UK). A standard balloon catheter (Cook's intramucosal catheter; Cook Urological Inc., Spencer, IN, USA) was passed through the vagina and cervical canal into the uterine cavity and the balloon was then filled with 0.5–1.0 ml of sterile saline. Once in position, the balloon was pulled tightly against the inner cervical ring in the uterine cavity.

Transvaginal ultrasound B-mode scanning using a 6 MHz probe was first performed to locate the uterus and ovaries (Toshiba SSA-270A, PVF-651 VT, Toshiba Co., Tokyo, Japan). The pouch of Douglas was examined to determine the presence of fluid before and after TSSG. A longitudinal view of the uterus was then taken and

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Table I. Patient demography and technical characteristics of transvaginal salpingosonography (TSSG) using air and Echovist®

<table>
<thead>
<tr>
<th>TSSG patients</th>
<th>Group A (air)</th>
<th>Group B (Echovist®)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>28 (4)</td>
<td>30 (5)</td>
<td>ns</td>
</tr>
<tr>
<td>Previous PIDS</td>
<td>5</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Previous operations*</td>
<td>8</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous tubal pregnancies</td>
<td>2</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Previous endometriosis</td>
<td>2</td>
<td>5</td>
<td>ns</td>
</tr>
<tr>
<td>Primary/secondary infertility</td>
<td>11/5</td>
<td>12/4</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of injection, min (SD)</td>
<td>10 (5)</td>
<td>7 (4)</td>
<td>ns</td>
</tr>
<tr>
<td>Contrast medium injected, ml (SD)</td>
<td>10 (5)</td>
<td>8 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*Gynaecological operations, appendectomy, bowel operations etc.
ns = not significant.
Previous PIDS = previous pelvic inflammatory diseases.

Categorical data were analysed using 2×2 frequency tables, the chi-squared test and Cohen’s kappa coefficient. Kappa (κ) is a chance-adjusted measure of agreement between two raters (i.e. observers) and can be defined as follows: observed agreement – chance agreement/potential agreement beyond chance. This has a theoretical maximum value of 1 when agreement is perfect. If the kappa value is between 0.60 and 0.80, the result can be regarded as substantial (Altman, 1991; Brennan and Silman, 1992; Byrt et al., 1993; Armitage and Berry, 1994). In addition, the performance characteristics for each method were calculated. P < 0.05 was considered to be statistically significant.

Results

A detailed patient demography, the mean duration of each method, as well as the mean amount of contrast medium used in each procedure are shown in Table I. There were more previous operations in group A (air-saline) than in group B (Echovist®) which was also a statistically significant finding (P = 0.02). TSSG was not technically satisfactory due to poor visualization in four tubes (two Fallopian tubes in group A and two in group B) and these were thus excluded from the final analysis. One patient in group A had been treated previously with unilateral salpingectomy because of a tubal pregnancy and therefore the total number of tubes examined was 29. No infections were reported after the procedure.

Ultrasound visualization of the flow in the Fallopian tubes was possible, but difficult, in five cases in group A and in two in group B. Patient compliance was good. The pain was usually described as being similar to the pain experienced during menstruation. The procedure, however, had to be interrupted in two cases (one in group A and one in group B) due to nausea and a strong and persistent pain.

Altogether 29 tubes were examined in group A (air). Of these, 21 tubes were patent and eight occluded at laparoscopy (Table II). Tubal occlusion had been observed in five out of 29 tubes after the TSSG examination. Concordance was thus 90%. Total disagreement between TSSG and laparoscopic chromatoperturbation was found in three tubes in this group. The sensitivity of TSSG was 63% and specificity 100%. The agreement between TSSG and chromatoperturbation was good in light of Cohen’s kappa coefficient, which was 0.71 (95% confidence interval (CI): 0.64–0.77).
Table II. Agreement between transvaginal salpingosonography (TSSG) using air and laparoscopic chromoperubtation in the detection of tubal patency in all (n = 29) Fallopian tubes in 16 patients (group A)

<table>
<thead>
<tr>
<th>TSSG</th>
<th>Chromoperubtation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occlusion</td>
<td>Patent</td>
</tr>
<tr>
<td>Occlusion</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Patent</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

Concordance, 90%, kappa 0.71 (95% confidence interval: 0.64-0.77), sensitivity 83%, specificity 100%, positive predictive value, 100%, negative predictive value, 98%.

Table III. Agreement between transvaginal salpingosonography (TSSG) using Echovist® and laparoscopic chromoperubtation in the detection of tubal patency in all (n = 30) Fallopian tubes in 16 patients (group B)

<table>
<thead>
<tr>
<th>TSSG</th>
<th>Chromoperubtation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occlusion</td>
<td>Patent</td>
</tr>
<tr>
<td>Occlusion</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Patent</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
</table>

Concordance, 93%, kappa 0.71 (95% confidence interval: 0.67-0.76), sensitivity 60%, specificity 100%, positive predictive value, 100%, negative predictive value, 93%.

Tubal occlusion was found in only in five out of 30 tubes at laparoscopy in group B (Echovist®) (Table III). Tubal occlusion had been diagnosed in TSSG in three out of 30 tubes in this group. They all were also observed to be occluded in laparoscopy. Concordance was 93%. Total disagreement was found in two tubes. The sensitivity of TSSG in group B was 60% and the specificity 100%. Cohen’s kappa coefficient was 0.71 (95% CI: 0.67-0.76) for this group.

Bilateral tubal occlusion was observed at laparoscopic chromoperubtation in three cases which were referred directly to the IVF programme. Bilateral tubal patency was observed in 19 cases. Unilateral tubal patency with contralateral occlusion was found in 10 cases.

Discussion

Both air and Echovist® were shown to be reliable contrast media in the assessment of tubal patency in this study. Concordance was shown to be both high and comparable, 90-93%, with both contrast media. Both techniques can be regarded as a reliable technique using Cohen’s kappa coefficient, which was the same in both groups, i.e. 0.71.

The comparison of different methods for assessing tubal patency is difficult. First, there are differences between individuals in different study populations. The visualization of the genital status with ultrasound scanning is also dependent on the location of the uterus, air-consistency of the bowel, the amount of fat in the lower abdominal cavity and the location of the ovaries in relation to the uterus. Second, the Fallopian tubes are sensitive to both manipulation and to fluids which easily cause spasms and pain which subsequently may cause a suspicion of occlusion. Methodological discrepancies may therefore appear between TSSG results and those for laparoscopic chromoperubtation in this type of study design. Due to the false positive results, not even laparoscopic chromoperubtation is 100% reliable for testing tubal patency, especially when unilateral tubal patency and contralateral occlusion is observed. The contralateral tube may still be unoccluded, but the passage of methylene blue may go in the direction of least resistance. There may also be technical problems in TSSG, for example the balloon of the catheter may not stay in position or visualization may be poor due to a retroverted uterus or the location of the ovaries just adjacent to the uterus, which makes the interpretation of tubal patency difficult, sometimes even impossible.

The sensitivity in both groups in the present study was low compared with our previous studies on TSSG (Heikkinen et al., 1995; Spalding et al., 1997). One possible explanation may be the high rate of occlusions observed in laparoscopy. Altogether, 13 out of 59 Fallopian tubes were observed to be occluded at laparoscopy. According to our study, the repeatability of TSSG is reduced by occlusions (Tekay et al., 1997).

The possibility of a tubal spasm cannot be neglected in the evaluation of tubal patency. In some cases, there was a clear discrepancy in diagnosing tubal flow by our method. For example, three Fallopian tubes were macroscopically normal, but demonstrated no flow at laparoscopy, i.e. a proximal occlusion was diagnosed. The contralateral tubes were patent. In these same cases using TSSG with air, however, flow was observed proximally, but not distally. In one case with a bilateral tubal occlusion observed at laparoscopy, fluid was observed in the free abdominal cavity after TSSG as an indirect sign of at least unilateral tubal flow. It must be remembered that with TSSG the demonstration of tubal patency is easy, but difficulties occur in distinguishing between a true distal occlusion and a benign spasm (Heikkinen et al., 1995; Spalding et al., 1997; Tekay et al., 1997). In a previous study by Bloechle et al. (1996), it has been suggested that when a proximal tubal obstruction is suspected in HCoSy, a sonographically controlled tubal catheterization could be performed. Using this method, functional tubal spasms could also be ruled out.

According to our results, both contrast media have their advantages and disadvantages. The long-term effects of Echovist® are not properly known. This medium was originally developed for i.v. use. No allergic-type reactions for Echovist® have been reported so far, but galactose allergy is a contraindication for its use. Adverse reactions other than pain (vasovagal reactions, nausea, vomiting, hyperventilation and sweating) have been recorded in 5% of cases. A discomfort or mild or moderate pain is usual. As air and saline are physiological substances, it is unlikely that these could have any long-term effects. Echovist® is slightly more echogenic than air. Its use may therefore be preferred in some patients with a poor visualization. On the other hand, its strong echogenicity may also be a disadvantage. For example, visualization of the posterior uterine muscle wall and the uterine cavity itself with Echovist® is poor as it causes a strong
backscatter effect with its acoustic shadowing (Figure 1). In place of Echovist®, saline is useful for the visualization and detection of polyps, submucous myomas and septa in the uterine cavity. It is therefore used in combination with air. It also improves the flow of air bubbles in the Fallopian tubes.

Two other disadvantages connected with Echovist® are its availability and price. It is not yet commercially available in all countries. One ampoule of Echovist® costs about $100 US and contains 20 ml of contrast medium, which is the recommended amount for one patient. The price of the catheters used in TSSG can vary from $7 to $70 US. If, however, we compare this to the costs of laparoscopic chromopertubation (~$900 US), both contrast media and all the other costs connected with TSSG are relatively inexpensive. It should be stressed that TSSG can be performed on an outpatient basis without hospitalization and with a short recuperation period. After the procedure, the patient is able to return to her normal daily routines immediately (Spalding et al., 1997).

There were no statistically significant differences in the mean duration of the procedure whether performed with air or Echovist®. TSSG can be regarded as a rapid and easy procedure. The mean injection time with both contrast media was only ~10 min. The entire procedure, including genital disinfection and insertion of the catheter, takes 15–30 min, depending on the patient.

In general, patients were content with TSSG. Even though patients in both groups complained of some pain sensation during the procedure, it was only necessary to interrupt the procedure in two cases. The menstrual-like pain described during the procedure may be due to expansion of the uterine cavity. This can be prophylactically treated with a prostaglandin inhibitor given 1 h before the procedure.

In this study, we were not able to demonstrate any statistically significant differences between air and Echovist® as contrast media used for TSSG. They are both easy to use for testing tubal patency. TSSG with these media is a reliable, safe and cost effective method as a primary phase examination method for tubal evaluation in infertile women.

References


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