Hysterosalpingo-contrast-sonography (HyCoSy) – a novel approach to female upper genital tract imaging and tubal patency assessment in outpatient clinic

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Abstract

Approximately 15% of couples in reproductive age are affected by the inability to conceive and bear a child. Anatomical disturbances are responsible for 35-40% of female subfertility. Frequent organic causes of sterility and infertility are linked to the fallopian pathology. Standard female screening procedures of infertility include imaging techniques. Tubal patency is routinely assessed by hysterosalpingography (HSG) and diagnostic hysteroscopy and/or laparoscopy. Other technologies are nowadays intensively investigated to obtain the satisfactory balance of diagnostic/therapeutic accuracy and cost-effectiveness. Such a promising novel method seems to be hysterosalpingo-contrast-sonography (HyCoSy), which is based on the ultrasonographic (US) evaluation of a female pelvis with contrast media substances infused intratunely. It could be performed on outpatient basis in many cases, reducing the need for a diagnostic hysteroscopy and/or laparoscopy. However, distention of uterine cavity with contrast medium used during HyCoSy procedure may be associated with a kind of unpleasant sensation, discomfort or even unacceptable pain. The superiority of ultrasonographically based HyCoSy occurs in terms of the lack of ovarian irradiation and avoiding allergy due to iodinated contrast used during HSG. Additionally HyCoSy enables scanning of the uterus and ovaries at the same time which is not available in HSG.

HyCoSy showed concordance with laparoscopy in 85.2% while HSG in 84.1%. New contrast media for ‘harmonic imaging’ in contrast-specific scanning and organ-specific contrast agents will significantly improve diagnostic possibilities in the nearest future.

Key words: sterility and infertility, female pelvis imaging, tubal patency assessment, hysterosalpingography (HSG), hysteroscopy/laparoscopy, hysterosalpingo-contrast-sonography (HyCoSy)

Introduction

Along with civilization development the phenomenon of sterility and infertility increases. It is estimated that approximately 15% of couples in reproductive age are affected by the inability to conceive and bear a child. About 60% causes are caused by a female factor, 30% originate on male side and the rest 10% derive either from immunological or unexplained sources. Endocrinologic dysfunction and endometriosis affect women in 30-50%, whereas anatomical disturbances are responsible for 35-40% of female subfertility [23]. The success at achieving conception in the infertile couple with anatomical abnormalities is currently very likely and available due to endoscopic correction [24].

Modern standard female screening procedures of infertility include imaging techniques, hormonal status evaluation and microbiological testing. Frequent organic causes of sterility and infertility are linked to the fallopian pathology. Tubal patency is routinely assessed by hysterosalpingography (HSG) and diagnostic hysteroscopy and/or laparoscopy (Hys/Lap). However, relatively high costs of these methods as a first line management are stressed. Therefore other technologies are nowadays intensively investigated to obtain the satisfactory balance of diagnostic/therapeutic accuracy and cost-effectiveness. One of such a promising novel method appears to be hysterosalpingo-contrast-sonography (HyCoSy), especially in terms of a screening test for subfertile patients [8]. Moreover, it could be performed on outpatient basis in many cases, reducing the need for a diagnostic hysteroscopy and/or laparoscopy [3].

HyCoSy – basic information

HyCoSy-contrast-sonography (HyCoSy) is based on the ultrasonographic (US) evaluation of a female pelvis with contrast media substances infused intratunely, which are regarded to significantly improve the diagnostic possibilities. HyCoSy in fact combines the transvaginal ultrasonography (TVS), saline infusion sonohysterography (SIS) and contrasted sonosalpingography [5, 32].

HyCoSy – description of the procedure

1) Device requirements

In order to perform HyCoSy examination one has to be equipped with TVS scanning machine (optionally abdominal transducer is necessary in certain cases), intrauterine catheter, contrast medium with applicator (a pump or a syringe) and data storage system (e.g. printer). Relevant complementary guidelines have been established recently in details [2, 7].

2) Steps of HyCoSy procedure

a) Transvaginal (Ultra)Sonography (TVS)

With a patient lying in a feasible position standard TVS of pelvis is performed, visualizing and detailing internal genital organs from the cervix through uterus to adnexa, with adequate measurements and descriptions (printed documentation is recommended).

b) Saline Infusion System (SIS)

In this step a sterile intrauterine catheter is introduced through the vagina and cervix. After proper fixation of the catheter is confirmed, the first contrast is infused (usually sterile saline solution) for more reliable visualization of uter-
rinary cavity and endometrial layers. This part of the examination is called Saline Infusion Sonography and may be accompanied by some kind of patient discomfort due to uterine and fallopian distention with fluid. The contrasted uterine space images are suggested to be stored for further reevaluation.

c) Hysterosalpingo-Contrasted Sonography (HyCoSy)

Finally, when satisfactory scans of SIS application are obtained, the last step takes place. Another contrast (usually air bubbles) is transferred into uterus using the same catheter still being at the same position within uterine space. This allows assessing and visualizing tubal structure and patency. The air bubbles or alternative contrast agents (e.g. Echovisist®), which are allocated to enhance the differentiation, provide more recognizable pictures of the fallopian lumen. Hence, the tubal structure assessment constitutes the particularly dedicated indication for that part of female genital tract investigation. In fact this is the real hysterosalpingo-contrasted sonography. In some situations only one positive contrast is used i.e. Echovisist® without saline or air. This modification although reasonable, increases costs of the examination and at least theoretically, constitutes danger of allergy.

If available, the movie proving contrast passage or any blockade of the flow through examined tubes should be recorded. At the end the catheter is removed after the rest of the contrast substance is spilled out of the uterine cavity.

Advantages of application of the new method

TVS allows visualizing internal female genital organs with adjacent structures in female pelvis and help differentiate especially solid or cystic masses. Application of SIS enables to distinguish abnormalities of endometrium and intracavitary pathology more precisely than TVS alone. Finally, introduction of another positive contrast medium apart from sterile saline solution permits to assess tubal patency with high accuracy [36].

HyCoSy joins the advantages of ultrasonographic evaluation of female pelvis and hysterosalpingographic assessment of fallopian tubes [22]. Because HyCoSy includes TVS and SIS it also possesses diagnostic value of the both techniques in the infertile couple investigation [16]. In comparison to HSG there are no significant differences between the two methods concerning the patient discomfort, duration of the procedures and the volume of contrast media required to visualize the fallopian tubes [4]. The superiority of ultrasonographically based HyCoSy occurs in terms of the lack of ovarian irradiation and avoiding allergy due to iodinated contrast used during HSG. Additionally HyCoSy enables scanning of the uterus and ovaries at the same time which is not available in HSG. These findings make HyCoSy more suitable for outpatient examination of subfertile women.

Comparing HyCoSy and HSG concordance with laparoscopic dye perturbation, the same high rate (86.7%) was found with 89.6% agreement between HyCoSy and HSG [14]. According to these evidence HyCoSy appears to be inexpensive, quick and patient well tolerable diagnostic method of determining the tubal status and uterine cavity at the time of conventional US scan is performed in place of HSG and pelviscopy.

HyCoSy — theoretical considerations

Adequate approach to HyCoSy methodology should also consider some restrictions, difficulties and complications. Selected technical and clinical situations are listed in table 1.

<table>
<thead>
<tr>
<th>Table 1. Limitations and complications during HyCoSy examination</th>
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<tr>
<td>1) Genital tract infections</td>
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<td>2) Cervical stenosis</td>
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<td>3) Endometrial cells spread (endometriosis, endometrial carcinoma)</td>
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<td>4) Contrast allergy</td>
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<td>5) Patient discomfort (pain induction)</td>
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<td>6) Vasovagal reactions</td>
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<td>7) Congenital abnormalities</td>
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<td>8) Menstrual/abnormal uterine bleeding</td>
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It seems to be obvious but worthy to mention that vaginal and cervical infections should constitute a contraindication to HyCoSy procedure except of step 1 (TVS alone). The recent guidelines even recommend disinfection of sonographic probe because the absolute certainty of latex membrane protection cannot be guaranteed. Also prophylactic antibiotic treatment is suggested prior intracavitory contrast infusion [2, 7].

HyCoSy may not be applicable due to primary or post-traumatic cervical stenosis [14]. In such occasions careful management is advised regarding desired pregnancy and cervical incompetence.

Endometrial cancer cells transfer to peritoneal cavity is quite unlikely in the infertile group of usually young patients but malignant elements were found in fallopian spilled fluid during evaluation of abnormal uterine bleeding [1]. Spread of cervical cancer by HyCoSy seems to remain rather in theoretical speculations.

Allergic reactions to the contrast media like air bubbles, Echovisist® and albumins are also questionable although far less reliable than during HSG when iodinate agents are used [6]. Latex irritation should concomitantly be reviewed in anamnesis.

Much more frequently reported adverse-events are patient's discomfort or even pain ranging from peridural to unbearable. 26% women experienced severe protracted pain and/or vasovagal reactions with bradycardia and hypotension. One third of the subjects required resuscitation with atropine owing to prolonged symptoms [31]. In some cases disturbing vaginal bleeding may occur following upper genital tract contrasting [34].

Congenital abnormalities of the cervix and uterus (e.g. uterus duplex) are also confusing situations leading to false conclusions or even preventing the HyCoSy examination to be
adequately performed and fully completed. In such occasions caution is urged as benefit may be obtained in endoscopic management rather than forceful HyCoSy introduction.

Physiological (menstruation) or abnormal (pathological) uterine bleeding may potentially be responsible for endometrial cells implantation and development of endometriosis within peritoneal cavity. Thus, timing the HyCoSy is established during the follicular phase (till 10th day) and special precautions are warranted in pathological bleeding [37].

Evidence Based Medicine (EBM) about HyCoSy

Tubal patency is nowadays most frequently examined via hysterosalpingography and by chromopertubation during laparoscopy. The experimental data suggest an important and significant role of HyCoSy in the process of upper genital tract imaging in comparison with above mentioned standard methods in the infertile women’s evaluation.

HyCoSy provided clinically valuable information about tubal patency, ovarian pathology and uterine abnormalities as first-line outpatient investigation in fertile units. The technique allowed detecting the presence of uterine abnormalities in 18% (fibroids, structural deviations and polyps findings), blocked tubes in 21% (8% could not be assessed due to technical reasons) and ovarian pathology in 6% (PCOS and cysts) among 132 infertile patients. Authors found this examination as simple and well tolerated procedure [5]. When HyCoSy was compared with HSG, no significant differences were found concerning technical background (duration of procedures and contrast consumption) or side-effects profile (patient pain and discomfort) with superiority of HyCoSy regarding the lack of X-ray exposure [4].

Contrasted sonography revealed agreement with HSG in proximal and distal patency of tubes in 82.9% and 82.1%, respectively while concordance in tubal occlusion in corresponding (proximal and distal) fallopian sections was 91.7% and 60%, respectively [22]. That explains why HyCoSy could be treated as highly efficient evaluation of tubal pathology and successfully applied as a non-invasive screening method. Strandell et al. [33] established significant reduction in both time and cost in HyCoSy based simplified infertility protocol versus routine management. Total diagnosis agreement in 74% and partial correspondence in 13% were sufficient to suggest adequate therapy in 38% of 99 subjects. However, Dijkstra et al. [13] found no strong arguments to replace HSG by HyCoSy or to reject HyCoSy in fallopian pathology assessment as both methods were compatible in tubal patency evaluation, pain experience and preferences in a group of 100 women.

Contrary to the positive data about HyCoSy, Stacey et al. [31] stressed its diagnostic accuracy, costs and patient’s discomfort as unfavorable compared with HSG. In this study group of 118 patients more severe adverse events (pain and vasovagal reaction with the necessity of resuscitation) were reported in HyCoSy as well as more technical failures were noted. Similarly, Bourghete et al [6] recognized air-contrast HyCoSy as less correct to HSG in the screening of infertile subjects. Only the use of special contrast medium enabled to reach the same accuracy as standard approach.

In several studies all the three methods (HyCoSy, HSG and laparoscopy) were concomitantly compared. HyCoSy demonstrated normal anatomy and tubal patency with sensitivity of 88% and specificity 100% for the right tube and 90% and 100% for the left one, respectively. The high reliability permits advance selection of women requiring more invasive diagnostic steps [28] and promotes usefulness in early sterility diagnosis as easy, quick and low-risk outpatient examination [9].

Similar positive opinions of HyCoSy as a valuable test for scheduling the most suitable treatment of infertile couples arouse when correlation of kappa values were found 0.48 for patency and 0.67 for detection of at least one patent tube. Meanwhile HyCoSy presented significantly lower sensitivity (50%) but not a significantly higher specificity (75%) than transvaginal sonography in tubal infertility-related adhesions [16].

A large meta-analysis of 1007 patients established concordance of 68.7% between HyCoSy and laparoscopy when patients were taken into account or 83.1% if tubes were investigated. False patency rate was 6.7% and false occlusion occurred in 10.3%. The same comparison for HyCoSy versus HSG was 68.3%, 83.3%, 3.9% and 12.8%, respectively. HSG occurred worse agreement than HyCoSy when compared with laparoscopy as the corresponding findings were 63.6%, 76.3%, 11.2% and 12.5% respectively [18].

As reliable and safe modality for evaluating tubal patency, especially suitable as an outpatient diagnostic procedure before more invasive methods, HyCoSy showed concordance with laparoscopy in 85.2% while HSG in 84.1%. Sensitivity was 85.2% for the two methods, specificity minimally higher for HyCoSy (85.2% vs 83.6%) as well as PPV (71.7% vs 69.7%) and NPV (92.9% vs 92.7%). Co-positivity and co-negativity was 66.7% and 81.8% between HyCoSy and HSG respectively, so in some cases HyCoSy may replace HSG to select women with patent tubes for infertility treatment without more invasive investigation. HyCoSy and HSG provided similar information about the status of endometrial cavity pathology (90% concordance) and tube pathology (72%), although HyCoSy more often found evaluation of fallopian pathology as uncertain while HSG more frequently classified tubal occlusion. Sensitivity and PPV were lower in HyCoSy than HSG (27% vs 75% and 88 vs 94%, respectively), specificity equal (90% vs 87%) whereas PPV higher (75% vs 47%) [32].

The recent study comparing HyCoSy, HSG and laparoscopy supported former observations that contrasted sonography is inexpensive, quick and well-tolerated method giving the advantage of obtaining information on tubal status and uterine cavity at the same time as conventional ultrasound scanning is performed. HyCoSy had the same concordance with laparoscopy as HSG (86.7%) and 89.6% when HyCoSy faced HSG [14].

In studies evaluating HyCoSy versus laparoscopy as golden standard, sensitivity ranged between 88-100%, spe-
cificity 55.6-82%, PPV 58-80% and NPV 96-100% [29,35]. However, the endoscopic reference is quite expensive so women with normal HyCoSy and magnetic resonance imaging (MRI) findings are regarded to have normal pelvis and may not need routine surgical treatment [3] as agreement in uterine abnormalities and tubal patency is 80.4% and 80%, respectively [34].

HyCoSy and patient’s discomfort

Distention of uterine cavity with contrast medium used during HyCoSy procedure may be associated with a kind of unpleasant sensation, discomfort or even unacceptable pain. In comparison with HSG, contrasted sonography affected 75% (89/118) patients with discomfort ranging from 0 (no pain) to 2 (moderate) but one fifth (19.5%) experienced prolonged pain, while no severe adverse reactions occurred in 116 patients having hysterosalpingography performed by the same operators [31].

However, other studies found no differences in patients’ pain/discomfort feeling during the compared procedures [13, 22]. When HyCoSy was faced with chromolaparoscopy, the most common complaint was pelvic pain in 36.7% (22/60 patients) followed by other events like nausea in 5% (3/60) and incidentally vaginal bleeding in 3.33% (2/60), mainly related to catheter insertion [34]. In clinical trial with infertile women in approximately 50% of patients HyCoSy caused little or no pain, in 40% moderate pain and only a small part complained about serious discomfort (8%). In 3% the procedure was discontinued due to the pain intensity [29].

Interestingly, the significant correlation between patient’s discomfort and tubal patency was confirmed. Visual Analogue Scale (VAS) standardized questionnaire assessment revealed the lowest mean score in patients with patent tubes (4.6), higher in subjects with distal occlusion (6.0) and maximal in women with proximal pathology (8.7) [18, 22]. Although in HyCoSy discomfort and pain similar to period sensation are a rare event bothering 4.3% of patients with mild intensity and 10.1% with severe, only 18 women require simple analgesia [5]. The accompanying vasovagal reactions like nausea occur quite rarely (7%) and only occasionally demand treatment (1.9%) [18].

Ayida et al. [4] in specially designed study assessed tolerance of HyCoSy and HSG as outpatient tests in 66 infertile women. No significant differences were detected between the two methods concerning the frequency or severity of pain at different stages during and after the procedure or analgesia requirements. 84% patients reported pelvic pain as the most frequent side effect, of which 100% during HyCoSy and 85% during HSG described the feeling as less or equal to periods pain. Only 18% women (24% HyCoSy, 13% HSG) required simple non-steroidal analgesia. The moment of HyCoSy procedure was associated with pain in 56% of patients and 72% in HSG, while in the following 24 hrs the feeling was confirmed in 41% and 47%, respectively. In conclusion HyCoSy and HSG were equally well tolerated for evaluation tubal patency and uterine abnormalities without differences in mean time (12.1 ± 5.2 min versus 9.5 ± 4.8, respectively) and volume contrast-medium consumption (9.4 ± 5.2 ml versus 11.4 ± 8.4 ml, respectively).

Apart from contrast-related adverse events, the insertion of catheter may also contribute to patient discomfort. There were several types of contrast donors evaluated regarding cost, patient tolerability, physicians’ ease of use, reliability, time required for positioning and volume contrast necessary for sonohysterography. No statistical differences were established among the catheters although e.g. Foleycath was the cheapest but most difficult to place and required more time for correct positioning, while Goldstein catheter was the best tolerated by the patients [11]. Replacing the need for repetitive cervical irritation by the single use of CVS probe in women with cervical stenotic was also described [25].

Improvements of HyCoSy diagnostic power and impact

The most cost-effective contrast agent for HyCoSy appears to be sterile saline solution with air bubbles. It can also be regarded as the least allergic one. Additionally other positive contrasted media have been applied for HyCoSy procedure. One of the most frequently used is Echovist® (SHU-454). However, saline seems to be more appropriate for the SIS step (assessment of uterine pathology) whereas Echovist enhances the tubal patency evaluation [32]. The amplification of diagnostic accuracy can be also achieved either by stimulated acoustic emission (SAE) or advanced ultrasonographic technologies. The insonation of Levovist® (echo-enhancing contrast agent) with high acoustic power of ultrasoundographic machine leads to disintegration of microbubbles resulting in SAE. That phenomenon applied for HyCoSy proved high coefficient (kappa = 0.76, 95% CI 0.5 60.96) with HSG, allowing to visualize the free spilling from fallopian tubes into the peritoneal cavity [26]. Also air-filled albumin microspheres (Infuson®) engaged in other study, revealed higher correlation with correct diagnoses (p = 0.006) than air-saline contrast alone and the same as HSG [6]. Another contrast substance, sonicated human serum albumin (Albunex®), occurred agreement in 12 of 14 histopathologically examined tubes [17].

Color Doppler technique improves the diagnostic accuracy of HyCoSy in suspected tubal occlusion and provides more vivid documentation of free tubal passage. It is also potentially advantageous in cases of dislocated tubes which may therefore be detected more easily and quickly [10, 28]. High correspondence of Color Doppler HyCoSy with laparoscopic findings (82.5-92%) is quite convincing and promising for the future application as first-line diagnostic work-up with infertile women [12, 19, 21]. Color Power Doppler HyCoSy proved to be superior to conventional HSG in evaluating adjacent myometrial structures, adnexa and follicular maturation; equal to HSG in visualizing the passage of the contrast medium into abdominal cavity but inferior to HSG in imaging the fallopian tubes owing to their tortuosity [15]. However, it seems to be
resolved when 3D technique is added for examination which enables better assessment of uterine cavity than HSG (detection in 96% vs 64%, \( p < 0.005 \)) and acceptable prediction of tubal patency by 3D HyCoSy with positive predictive value of 100%, negative predictive value in 33.3%, sensitivity 84.4% and specificity of 100% to HSG as a reference [20]. On the other hand, 3D Power Color Doppler HyCoSy improves even more the tubal visualization (91% vs 46%) and decreases contrast volume consumption in comparison to 2D HyCoSy. That modality of HyCoSy might have better side-effect profile and provide convenient storage of data [30] but is no longer cost-effective in outpatient office.

**Future perspectives and developments of HyCoSy**

It can be expected that pressures from insurance companies to reduce costs of medical management will result in novel approaches. HyCoSy already nowadays meets several desired criteria for cost-effective, reliable and acceptable method as a component of first-line infertility screening available on outpatient basis. Moreover, wider horizons are opened in front of the technique enhancing its diagnostic and even therapeutic potential.

First, new contrast media for so-called ‘harmonic imaging’ in contrast-specific scanning and organ-specific contrast agents will significantly impact diagnostic possibilities in the nearest years to come [27]. Then, the combination of HyCoSy with fine, flexible endoscopic device guided through the infusion catheter would expand the recognition of upper genital tract morphology, physiology and infertility factors especially within intratubal lumen. This may also broaden the use into therapeutic approach e.g. intratubal or intnutubal adhesiolysis. Such futuristic visions may not have to be very unlikely as there are already similar procedures called percutaneous and transcervical falloposcopy, currently undergoing clinical trials [36].

Thus, the enriched HyCoSy could therefore be recognizable as **Hysterosalpingo-contrast sonography** in which not only the infertility cause is identified but also adequately treated either by the passage restoration or finally even with GIFT or ZIFT in assisted reproductive technology/technique. But still would it be cost-effective and outpatient available procedure in our offices?

**References**


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