ExEm® Foam Kit
Business Case – technical

V.3. 5/10/2015

Indication

All indications for creating foam for Hysterocontrast Sonography (HyCoSy).
NB: Also known as Hysterosalpingo Sonography
NB: The HyCoSy procedure performed with ExEm® Foam is referred to as HyFoSy in some literature

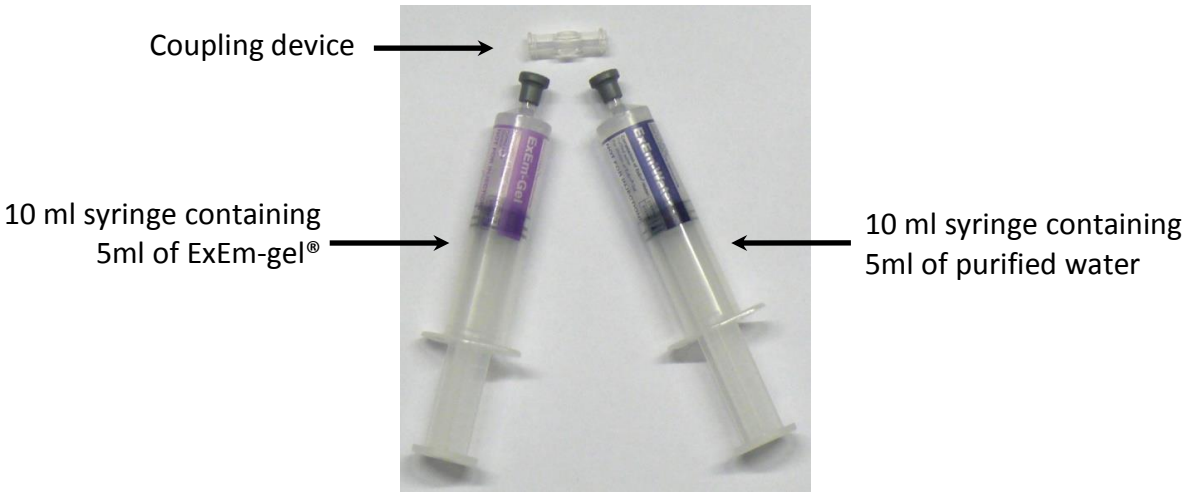
EU Certified medical device

The ExEm® Foam Kit consists of 3 parts:

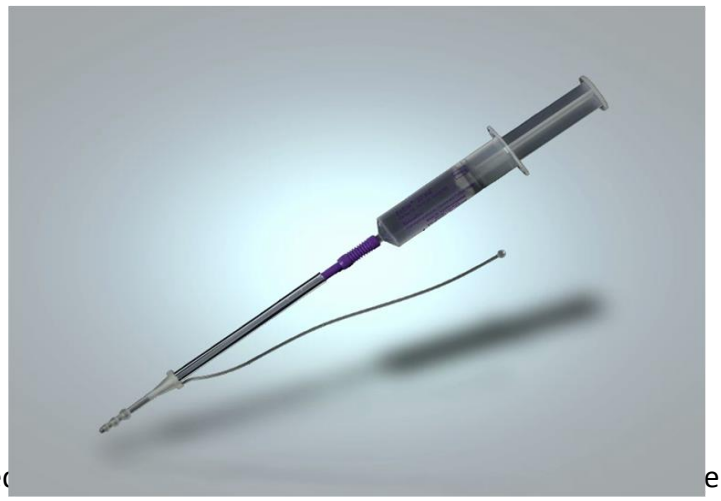
1. a 10 ml syringe containing 5ml ExEm-gel®
2. a 10 ml syringe containing 5ml purified water
3. a coupling device

An optional GIS catheter is also available

ExEm® Foam Kit



GIS catheter (optional)



All parts are EU certifie e Directive 93/42/EEC of 14 June 1993.

Scope of the CE-marking

The Directive applies to medical devices and their accessories according to the following definitions:
"Medical device" means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of *disease*,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an *injury or handicap*,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

General Requirements:
The device must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

The manufacturer must apply the following principles:

- eliminate or reduce risks as far as possible
- take adequate protection measures in relation to risks that can not be eliminated.
- inform users of the residual risks due to shortcomings of the protection methods adopted.

Depending on the type of medical device the manufacturer must additionally fulfil one or more Annexes (Annex II to XII) detailed in the Directive.

ExEm® Foam fulfils Annex V (production quality assurance), Annex VII (technical documentation) and Annex X (clinical data) as certified in enclosure 1 (CE Declaration of Conformity ExEm Gel).

10 ml syringe with purified water fulfils Annex V (production quality assurance), Annex VII (technical documentation) and Annex X (clinical data) as certified in enclosure 2 (CE Declaration of Conformity syringes purified water for dilution of ExEm-gel®).

Couplers fulfil Annex II (full quality assurance system) as certified in enclosure 4 (CE Declaration of Conformity Couplers).

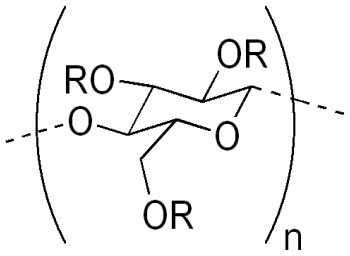
GIS catheter fulfils Annex II (Full quality assurance system except sec 4, product design dossier) and Annex V (only sterility aspects of production quality assurance) as certified in enclosure 5 (CE Declaration of conformity Gynetics GIS catheter).

Purpose

ExEm® is an EU certified medical device and CE marked for gynaecological intracavity ultrasound imaging and gel infusion sonography except intravenous applications:

Safety

Chemical structure of Hydroxyethylcellulose



$R = H \text{ or } CH_2CH_2OH$

Hydroxyethylcellulose (and methylcellulose) are frequently used with hydrophobic drugs. They are organic chemical compounds derived from cellulose. They are hydrophilic white powder in pure form and dissolve in cold (but not in hot) water, forming a clear viscous solution or gel. They are used as thickeners and emulsifiers in various food and cosmetic products. Because hydroxyethylcellulose is fibrous and water soluble, it can be used as an effective laxative in the treatment of constipation. Like cellulose, they are not digestible, not toxic and not allergenic.

As the ingredients of ExEm Foam are equal to ExEm-gel® allergy and complications are expected to be equally rare.

In this preferred embodiment the composition consists substantially of a cellulose derivative, hydroxyethylcellulose, in a buffer and no other adjuvants. It is important that the composition contains so much of the cellulose derivative to achieve a viscosity preferably between 2400 and 2500 mPa.sec. at body temperature. Using this composition high contrast 3-dimensional images and virtual hysteroscopy are obtainable. Three dimensional imaging requires a very stable and quiet filling of the cavity with a minimum amount of artefacts. The gel and HyFoSy method enables this.

Since its launch in 2010, there have been >15,000 (as @ Dec 2014) HyCoSy procedures performed the UK and Ireland with ExEm® foam. There have been no allergic reactions and no infections reported.

"No unknown side effects of gel or foam, or unexpected concerns about safety, were reported…. the combination of glycerol, hydroxyethyl cellulose and purified water is considered to be safe for intrauterine application and tubal patency testing, indicating an optimal risk–benefit ratio in clinical use" [(1)].

Further supportive safety data of hydroxyethylcellulose

A report on Safety Assessment of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum[(2)] published in the International Journal of Toxicology in 1986 the cellulose derivatives demonstrated no mutagenic activity in animal models. At concentrations up to 100% they were non-irritating to mildly irritating, non-sensitizing, and non-photosensitizing when evaluated in clinical studies. It is concluded that the ingredients reviewed are safe as cosmetic ingredients in the present practices of use and concentration.

…hydroxyethylcellulose as a placebo substance:

Hydroxyethylcellulose is a well-established placebo substance used in clinical trials in a variety of therapeutic areas. The chemical properties classify hydroxyethylcellulose as an emulsifier, stabilizer, water retaining and thickening agent. A useful placebo must be stable without altering the active

drug, and in itself must be safe and well tolerated. A recent study demonstrated the safety, stability, inactivity, and efficacy of hydroxyethylcellulose as a universal placebo for clinical trials of microbicides[3].

Within a publication from 2009[4] the Department of Reproductive Health and Research, WHO further state: "The placebo must be tested in appropriate systems to ensure its safety and its lack of activity on HIV and other STI pathogens. A so-called "universal" placebo based on an aqueous preparation of hydroxymethyl cellulose, lacking both anti-infective potency and buffering capacity, has been developed" [5]

In an HIV prevention study[6] conducted between 2005 and 2008 among 3099 HIV-negative women, the safety and effectiveness of 2 microbicides were tested against no treatment and a placebo treatment. The "non-perturbing" placebo consistent of 96% purified water and 2.7% hydroxyethylcellulose.

…hydroxyethylcellulose as a buffering gel:
PGE2 in a gel of hydroxyethyl cellulose was tested in a randomized double-blinded study[7] for cervical ripening. Administered by intra-cervical, intravaginal and extra-amniotic routes in a hydroxyethyl cellulose gel medium proving successful ripening of the cervix and no adverse side-effects.

Rationale

Tubal obstruction is estimated to play a role in 10% to 35% of infertile couples[8,9]. Assessment of fallopian tube patency is an important part of routine infertility work-up. Several test are available for this purpose

- hysterosalpingography (HSG)
- selective salpingography
- laparoscopy and dye test,
- hysterosalpingo-contrast sonography (HyCoSy)

Most commonly used echogenic medium was Echovist® however, this product withdrawn from sale by the manufacturer for commercial reasons in 2009. An alternative for Echovist® is to use air with saline. This is very cheap but there are problems involved with this as air escapes from the solution within seconds, actually most air bubbles have vanished at the moment of its injection[10].
In 2007 ExEm-gel® was introduced as a contrast medium for sonohysterography offering a more stable filling of the uterine cavity and very little inconvenience for the patient. It has been used for HyCoSy since 2010.

Background and mode of action of ExEm® Foam Kit

Medical diagnostic imaging is widely used for the examination of body cavities. A prerequisite for the imaging of body cavities is the instillation of a fluid in order to obtain a fluid-filled cavity. The fluid has two functions:

1. to open the cavity from its "collapsed" state (distension)
2. to enhance the contrast of the image of the body cavity

Conventionally, water or watery fluids are used sometimes combined with the generation of bubbles to further increase contrast. Since water easily leaks from the body cavity, it has to be replenished continuously during imaging. This disadvantage may be solved partly by using liquid instillation devices which reduce leakage.

With ExEm-gel®, a foam can be created when 5ml of gel is diluted with 5 ml of purified water.
The gel is pushed rigorously through small openings in syringes or tubings. The turbulence will cause local pressure drops resulting in air to dissolve in the solution in the form of little air bubbles.
These microbubbles form a foam that is stable for several minutes and has the ability to pass through patent fallopian tubes to determine patency.
During HyFoSy procedure the fallopian tubes will be reflected on the ultrasound. The tubes will be visible for a short period of time. If not, the passage of one or both of the fallopian tubes might be disturbed.

When the procedure is finished the foam that flows into the abdominal cavity will be processed by the human body. The remaining foam will be reabsorbed within 24 hours just like air remaining in the abdominal cavity after abdominal surgery.

How to prepare ExEm Foam

1. Dilute the 5 ml ExEm® gel with the 5 ml (purified) ExEm® water by mixing the fluids from one syringe through the coupling device into the other syringe (at least 10 times). This creates a gel foam.

2. Leave the gel foam in one syringe and disconnect the other syringe and coupling device.

3. Connect the syringe containing the gel foam to a suitable catheter and infuse the gel foam within approximately 5 minutes.

Effectiveness

HyCoSy (HyFoSy) performed with ExEm® Foam (hydroxyethylcellulose & glycerol mixed with purified water) has been shown to be an effective method of assessing tubal patency[11,12].

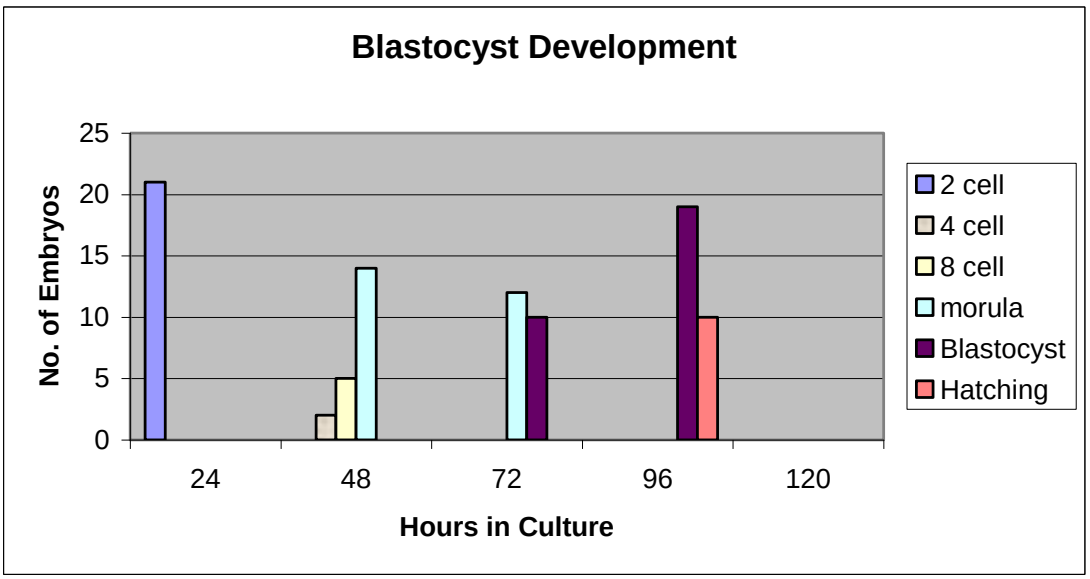
Toxicity ExEm-gel® and sterile pure water

A 1-cell stage embryo toxicity testing on ExEm-gel® (10ml) and Sterile ultra-pure water (as emulsion 1% solution) was performed in July 2010. The test is a release test and the product only marketed if it has passed the test. An equivalent test was performed for the GIS-catheter (next page) in March 2010.

Frozen-thawed mouse-embryos were cultured in IVF embryo growth medium with ExEm-gel® and water emulsion added for 120 hours (5 days). The gel proved to be non-toxic for embryos according to below defined test requirements:

Mouse Embryo	**Test Requirements for Passing**	**Result**
Control Assay Results:	≥80% 1 cell to blastocyst within 120 hrs	**96%***
	≥50% blastocysts hatching within 120 hrs	**53%***
Test Assay Results:	≥80% 1 cell to blastocyst within 120 hrs	**95%***
(see graph below)	≥50% blastocysts hatching within 120 hrs	**59%***

* Results after 96 hrs



Mouse Embryo Assay (MEA) test: **PASSED**

The test was prepared by: K.E.Tucker, Ph.D., HCLD (ABB), ELD (ABB)
Scientific Director, IVF Voorburg

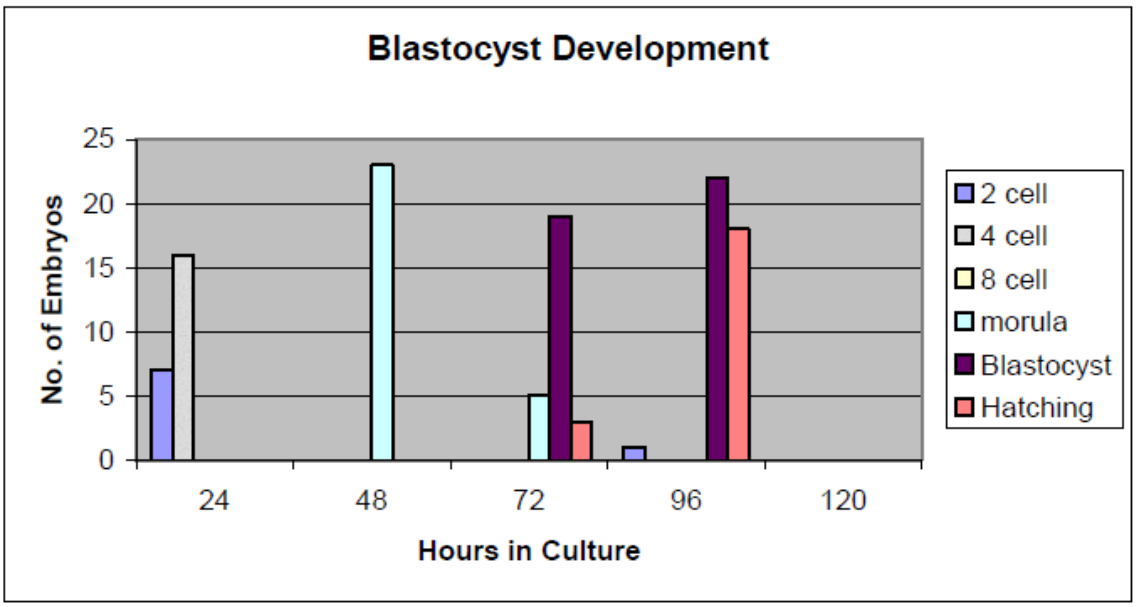
Date: July 20th 2010

Toxicity GIS-catheter

Frozen-thawed mouse-embryo were cultured in IVF embryo growth medium in a gassed, humidified environment for 120 hours (5 days). The catheter proved to be non-toxic for embryos according to below defined test requirements:

Mouse Embryo	**Test Requirements for Passing**	**Result**
Control Assay Results:	≥80% 1 cell to blastocyst within 120 hrs	**87%***
	≥50% blastocysts hatching within 120 hrs	**95%***
Test Assay Results:	≥80% 1 cell to blastocyst within 120 hrs	**96%***
(see graph below)	≥50% blastocysts hatching within 120 hrs	**92%***

* Results after 96 hrs



Mouse Embryo Assay (MEA) test: **PASSED**

The test was prepared by: K.E.Tucker, Ph.D., HCLD (ABB), ELD (ABB)
Scientific Director, IVF Voorburg

Date: March 11th 2010

Genotoxicity testing of ExEm-gel®

In 2009 Bioserv Analytik Und Medizinprodukte GmbH in Germany performed a genotoxicity test[13] (OECD 476) of ExEm-gel® to assess cytotoxicity of the extracts. The mouse lymphoma assay allows the evidence of gene mutations induced by chemical substances. During the extraction of the test material at 37°C over 24 hours, no substances were derived that cause genotoxicity under the test conditions of the mouse lymphoma assay.

A similar test (Salmonella typhimurium reverse mutation assay) was performed using S. typhimurium strains TA 97a, TA 98, TA 100, TA 102 and TA 1535[1]. Bacteria were exposed to the extract of the test material (ExEm-gel®) with and without metabolic activation system (S9-mix) and plated onto minimal medium. After incubation revertant colonies were counted and compared to the number of spontaneous revertants in an untreated and/or solvent control culture.
During the extraction of the test material by means of PBS as extractants at 37°C over 72 hours, no substances were derived that cause genotoxic activity during the course of the observation period as tested by the Salmonella typhimurium reverse mutation assay.

Cytotoxicity testing of ExEm-gel®

In 2007 Bioserv Analytik Und Medizinprodukte GmbH performed a cytotoxicity assay[14] according to DIN ISO 10993-5.

Test Material: Sterile ExEm®, silicone rubber of comparable weight (negative control) and 5% Dimethyl Sulfoxide (positive control medium).

Dilution medium was DMEM-FCS, prepared freshly. Cytotoxicity testing of the test material extract was performed at concentrations of:
a)100%
b) 66%
c) 44%
d) 30%
c) 20%

The degree of cytotoxicity observed was numerically graded using a subjective grading system as follows:
0: cell monolayer complete, no cell damages
1: cell damages visible, but not greater than in 25% of all the cells
2: more than 25%, but no more than 50% of all the cells are damaged or dead
3: cell damages or death in 50% to 75% of all the cells
4: cell death greater than 75% - the monolayer may be completely destroyed

Results:

Cells covered with DMEM-FCS freshly prepared or covered with DMEM-FCS incubated for 24 hours at 37° C did not show any damage (grade 0). Also the undiluted extract of the negative control material (silicone rubber) did not harm the cells (grade 0).

The positive control solution (5% DMSO dissolved in DMEM-FCS) caused, as expected, damages to more than 50% of the cells.

The extract of the test material, ExEm®, caused no toxicological / biological critical cell damages and growth inhibition. Under these conditions the test material is considered non-cytotoxic and meets the requirements of the DIN ISO 10993-5 (EN 30993-5).

Scientific overview

1. Safety aspects and side effects of ExEm gel and foam for uterine cavity distension and tubal patency testing

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Abstract A state-of-the-art overview of the safety and side-effects of ExEm-gel for uterine cavity distension and ExEm-foam for tubal patency testing is presented. A literature search was carried out using PubMed, textbooks, pharmaceutical databases and reports of toxicity tests. Information on clinical use in humans and experiments in animal models was collected and grouped according to the following components: glycerol, hydroxyethyl cellulose and purified water; subjects included toxicity test, influence on sperm cells, oocytes, blastocyst development, uterine cavity distension, tubal patency testing, pain and obstetric applications. No unknown side effects of gel or foam, or unexpected concerns about safety, were reported. More information than expected was available on the absence of effects of the components on various human tissues. Although it is difficult to prove that the search is complete, and it is possible that side-effects remain unreported, the combination of glycerol, hydroxyethyl cellulose and purified water is considered to be safe for intrauterine application and tubal patency testing, indicating an optimal risk–benefit ratio in clinical use. The safest strategy, however, is to restrict clinical examinations with gel and foam to the pre-ovulatory phase of the menstrual cycle.

11. First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing

Mark Hans Emanuel[1]*,*, Michelle van Vliet*[1]*, Maaike Weber*[1] *and Niek Exalto*[2]
1) Department of Obstetrics and Gynaecology, Spaarne Ziekenhuis Heemstede/Hoofddorp. PO Box no. 2130 AT Hoofddorp. 2) The Netherlands IDepartment of Obstetrics and Gynaccology, Division of Obstetrics and Prenatal Medicine Erasmus Me, University Medical Centre, Rotterdam, The Netherlands.

BACKGROUND: This study was conducted to describe the first experiences with hysterosalpingo-(oam sonography (HyFoSy) as a first step routine office procedure for tubal patency testing.
METHODS: A prospective observational cohort study was started in a university affiliated teaching hospital. In 20 I0, 73 patients with subfertility and a low risk of tubal pathology were examined. A non-toxic foam containing hydroxymethylcellulose and glycerol was applicated through a cervical applicator for contrast sonography (HyFoSy).Tubal patency was determined by trans-vaginal ultrasonographic demonstration of echogenic dispersion of foam in the Fallopian tube and/or the peritoneal cavity. Only in case patency could not be demonstrated, a hysterosalpingography (HSG) was performed as a control.
RESULTS: In 67 out of 73 (92%) patients, a successful procedure was performed. In 57 out of 73 (78%) cases, there was no further need for an HSG. In five patients (5/73; 7%) tubal occlusion was confirmed by HSG and in five patients (5/73; 7%) there was discordance between HyFoSy and HSG. Of 73 patients. 14 (19%) conceived within a median of 3 months after the procedure.
CONCLUSIONS: HyFoSy is a successful procedure to demonstrate tubal patency as a first step office procedure.

12. The Use of a New Gel Foam for the Evaluation of Tubal Patency

Dominique Van Schoubroeck, Thierry Van den Bosch, Christel Meuleman, Carla Tomassetti, Thomas D'Hooghe, Dirk Timmerman
Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven , Belgium

Aims: To evaluate the feasibility and the reliability of hysterosalpingo-foam sonography (HyFoSy) using gel foam in the assessment of tubal patency.
Methods: Nonrandomized, observational, academic and single-center study of 20 women being investigated because of subfertility and scheduled for a laparoscopy with chromopertubation. A detailed description of HyFoSy with a newly developed gel foam is given in the way it proved to be most efficient in our hands. The results of HyFoSy are compared to the data regarding tubal patency testing during laparoscopy by chromopertubation.
Results: All 20 HyFoSy were technically successful. Four of the 40 tubes, 1 right tube and 3 left tubes, were not patent at HyFoSy (3 tubes with proximal block and 1 tube with distal block). There was a 100% agreement between tubal patency data according to HyFoSy testing and laparoscopic chromopertubation testing.
Conclusion: HyFoSy is both feasible and accurate in the diagnosis of tubal patency.

15. Saline infusion versus gel instillation sonography: a prospective cohort study

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[1]Obstetrics & Gynecology, University Hospitals K.U. Leuven, Leuven, Belgium; [2]Electrical Engineering,ESAT-SCD, K.U. Leuven, Leuven, Belgium

Objective: The aim of this study is to compare saline infusion sonography (SIS) with gel instillation sonography (GIS) in terms of feasibility and diagnostic accuracy in patients with abnormal uterine bleeding.
Design: Observational cohort study
Patient(s): 804 patients. Two consecutive cohorts of 402 women undergoing SIS og GIS at the department Bleeding Clinic were included.
Patients characteristics, ultrasound features, technical failure rates and final diagnosis (based on endometrial sampling, hysteroscopy and/or surgery) were compared.
Pathology was defined as hyperplasia, polyps, intracavity myomas and carcinoma.
Result(s): Mean age was 50.7 years (SD 12) and 50.2 years (SD 11.6) in the SIS and GIS group (NS). In the SIS group 12.7% were nulliparous and 53% premenopausal versus 17.4% and 57.2% in the GIS group (NS). Technical failure rate was 5.0% for SIS versus 1.9% for GIS (difference between proportions 0.03; CI [0.0054-0.0588]). Failure due to inadequate distension was 1.5% versus 0.3% for SIS and GIS (difference between proportions 0.01; CI [−0.02 0.03]). Pathology was diagnosed in 180 (49%) patients of the SIS group versus 147 (40.2%) of the GIS group (difference between proportions 0.09; CI [0.02-0.16]). The LR+ and LR− of a lesion during contrast sonography was 4.03 and 0.28 for SIS and 3.9 and 0.19 for GIS, respectively (NS). The sensitivity was 77.8% and 85.0%, respectively (NS). The negative predictive value was 79.1% for SIS and 88.6% for GIS (difference between proportions 0.095; CI [0.02-0.17]).
Conclusion(s): The technical failure rate, partly due to unstable filling of the uterine cavity and transcervical backflow, was less for GIS. The diagnostic accuracy of GIS was comparable with SIS. We conclude that GIS is a feasible and accurate alternative for SIS in the evaluation of peri- and postmenopausal women with abnormal bleeding.

16. Foam Infusion Sonosalpingography (FIS) or Hysterosalpingo Foam Sonography (HyFoSy) or Hysterosalpingo Contrast Sonography (HyCoSy) with Foam

Mark Hans Emanuel MD PhD, Ineke Tromp MD and Julie Knieriem MD
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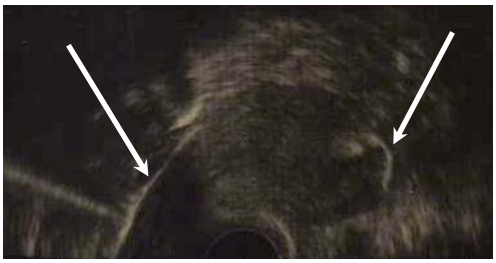
Objective: To describe and introduce a new technique of direct imaging of the tubal passage in tubal diagnostics of tubal patency during transvaginal ultrasonography.
Design: Descriptive study of a new technique.
Materials and Methods: A simple and cheap alternative is presented by mixing ExEm-gel® and purified water creating a foam with microbubbles. This foam can be infused through a catheter with cervical adapter that was developed for GIS.
Result(s): The findings and images obtained by HyFoSy showed an easy recognition of the tubal passage of the foam in case of tubal patency.
Conclusion: Tubal patency can be easily recognized by HyFoSy. It seems reasonable to expect that the use of HyFoSy will be an acceptable first step, cheap and simple screening method for tubal patency.



FIS or HyCoSy with Foam images of tubal patency (arrows)

A Randomised Controlled Trial has recently been conducted comparing SIS with saline versus GIS with ExEm®gel with a primary outcome of diagnostic accuracy and a secondary outcome of inconvenience for the patient and examiner, pain and costs:

17. The Diagnostic Accuracy of Gel Instillation Sonohysterography (GIS) Compared with Saline Infusion Sonohysterography (SIS); a Randomised Controlled Trial

Emanuel MH, Tromp I, Betlem M.
OB/GYN, Spaarne Hospital, Hoofddorp,The Netherlands

Objective: To compare the diagnostic accuracy of Gel Instillation Sonohysterography (GIS) with the diagnostic accuracy of Saline Infusion Sonohysterography (SIS).
Design: Prospective Randomised Controlled Trial.
Patients: Between Aug 2007 and Dec 2008 103 consecutive patients with abnormal uterine bleeding and an abnormal transvaginal ultrasound were recruited.
Materials and Methods: Patients were randomised for the use of Gel Instillation or Saline Infusion during Sonohysterography. Abnormalities detected during Sonohysterography were classified as pedunculated polyp, sessile polyp, pedunculated myoma (type 0), sessile myoma (type 1) and sessile myoma (type 2). Hysteroscopy was used as gold standard in case of abnormalities. The primary outcome measure was diagnostic accuracy.
Result(s): In the GIS group (n 5 53) 35 abnormalities were found; 31 (89%) were confirmed during hysteroscopy. In the SIS group (n 5 50) 30 abnormalities were found; 22 (73%) were confirmed during hysteroscopy. Suspected pedunculated polyps were confirmed during hysteroscopy in all 8 cases, sessile polyps in 15 out of 19 cases, pedunculated myomas (type 0) in 10 out of 14, sessile myomas (type 1) in 9 out of 13 and sessile myomas (type 2) in all 11 cases.
Conclusion: Gel Instillation is an alternative for Saline Infusion during Sonohysterography. Gel Instillation has a higher diagnostic accuracy than Saline Infusion during Sonohysterography.

18. Hysterosalpingo-foam sonography, a less painful procedure for tubal patency testing during fertility workup compared with (serial) hysterosalpingography: a randomized controlled trial.

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a Department of Reproductive Medicine, VU University Medical Center, Amsterdam; and b Department of Obstetrics and Gynecology, Spaarne Hospital, Hoofddorp, the Netherlands

Objective: To determine whether hysterosalpingo-foam sonography (HyFoSy) is a less painful first line tubal patency test than serial hysterosalpingography (HSG).
Design: A two-center, prospective, open-label, randomized, controlled trial.
Setting: University hospital and teaching hospital.
Patient(s): 40 subfertile women, ages 18 to 41 years, with an indication for tubal patency testing as part of the fertility workup according to the Dutch Nederlandse Vereniging voor Obsteterie & Gynaecologie-guidelines.
Intervention(s): Tubal patency testing by HyFoSy versus serial HSG.
Main outcome measures(s): Visual Analogue Scale (VAS) pain scores during tubal patency testing.
Result(s): The median VAS score for pain perception during the HyFoSy procedure was 1.7 cm (interquartile range: 2.1) compared with 3.7 cm (interquartile range: 4.2) during HSG. The HyFoSy procedure also had a statistically significantly shorter procedure time compared with HSG, with a median of 5.0 minutes (interquartile range: 3.0) for HyFoSy versus 12.5 minutes (interquartile range: 16.0) for HSG.
Conclusion(s): The HyFoSy procedure is a less painful and less time-consuming tubal patency test compared with HSG.

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