

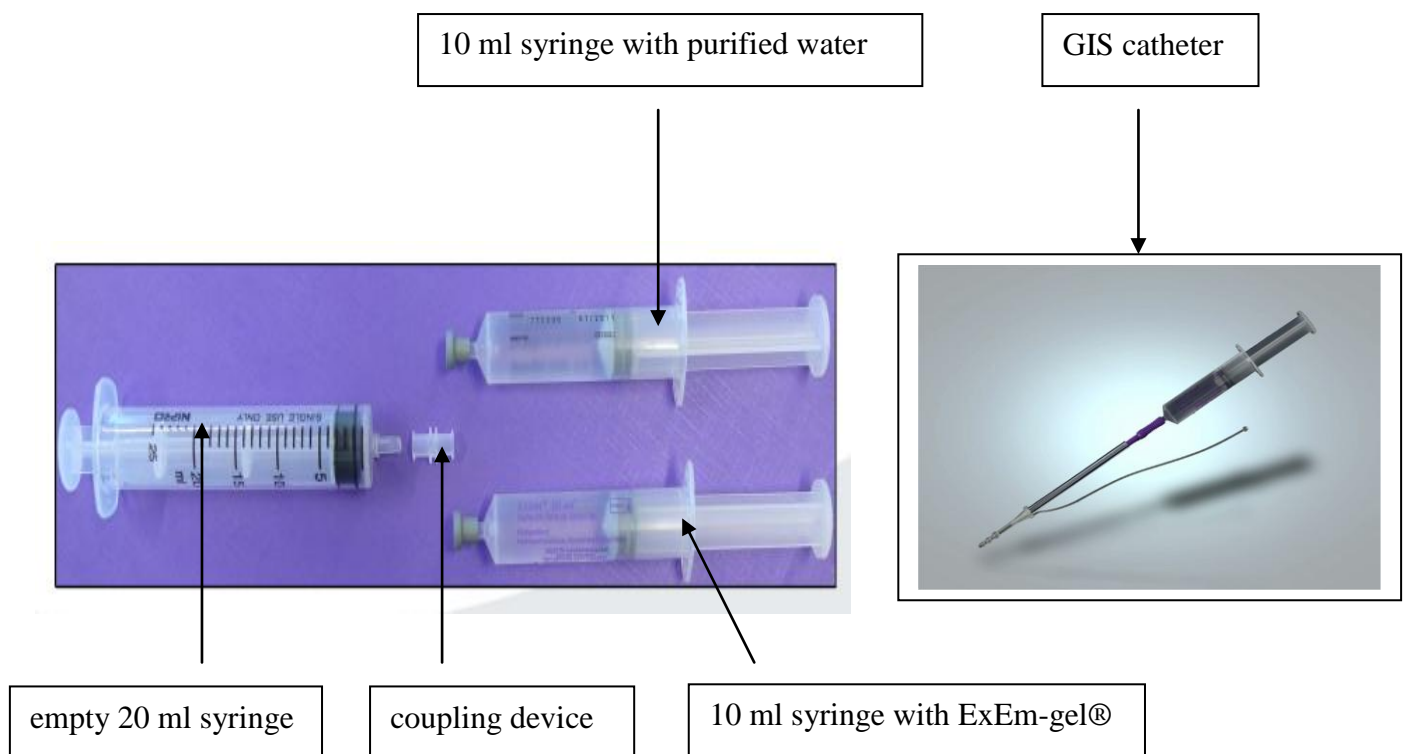
**Indication**

All indications for creating foam for Hysterosalpingo Sonography.

**EU Certified medical device**

The ExEm® Foam Kit consists of 5 parts:

1. a 10 ml syringe with ExEm-gel®
2. a 10 ml syringe with purified water
3. an empty 20 ml syringe
4. a coupling device
5. GIS catheter



All 5 parts are EU certified medical devices and comply with the Medical Device 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®).**

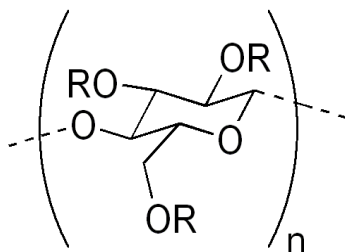
**20 ml syringe fulfils Annex V (production quality assurance), Annex VII (technical documentation) and Annex X (clinical data) as certified in enclosure 3 (CE Declaration of Conformity TPC syringe without needle).**

**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).**

## Safety

### Chemical structure of Hydroxyethylcellulose



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 2007 there has been >15,000 procedures in Europe with ExEm-gel®. There have been no allergic reactions and no infections reported.

### Further supportive safety data of hydroxyethylcellulose

A report on Safety Assessment of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum<sup>0)</sup> 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 nonirritating to mildly irritating, nonsensitizing, and nonphotosensitizing 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 (HPTN 035) [http://www.hptn.org/research\\_studies/hptn035.asp](http://www.hptn.org/research_studies/hptn035.asp) demonstrated the safety, stability, inactivity, and efficacy of hydroxyethylcellulose as a universal placebo for clinical trials of microbicides<sup>1)</sup>.

Within a publication from 2009<sup>2)</sup> 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” (*Tien D et al. In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials, AIDS Research and Human Retroviruses 2005, 21:845-853*) <http://www.ncbi.nlm.nih.gov/pubmed/16225411>

In an HIV prevention study<sup>3)</sup> 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-pertubing” placebo consisted of 96% purified water and 2.7% hydroxyethylcellulose.  
<http://www.hptn.org/Web%20Documents/HPTN035/05HPTN035PlaceboSumDurban.pdf>

### **...hydroxyethylcellulose as a buffering gel:**

PGE2 in a gel of hydroxyethyl cellulose was tested in a randomized double-blinded study<sup>4)</sup> for cervical ripening. Administered by intracervical, 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<sup>5,6)</sup>. Assessment of fallopian tube patency is an important part of routine infertility work-up. Several tests are available for this purpose

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

Most commonly used echogenic medium is Echovist®, however this product is no longer available.

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<sup>8)</sup>.

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.

The ExEm® Foam Kit and HyFoSy technique also enables verification of the correct placement of the micro implants after a sterilization procedure (Essure and Adiana).

## **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 the gel is diluted with 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 when diluted with 10 ml of purified water sufficient fluid to pass patent tubes.

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.

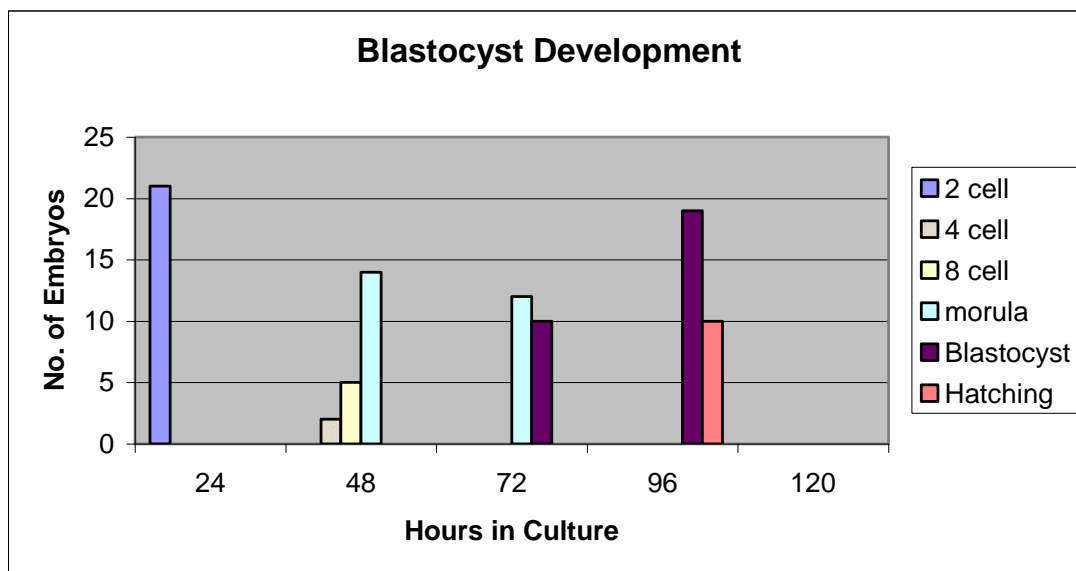
## Toxicity ExEm-gel® and sterile pure water

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:

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

\* 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

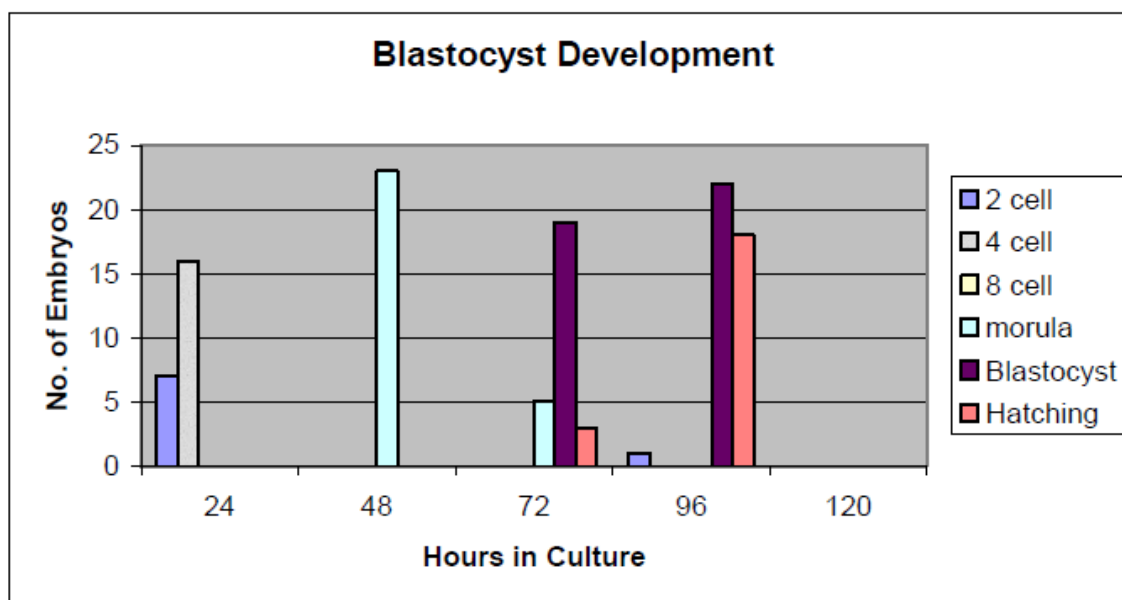
Date: July 20<sup>th</sup> 2010

## 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:

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

\* 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 11<sup>th</sup> 2010

## Genotoxicity testing of ExEm-gel®

In 2009 Bioserv Analytik Und Medizinprodukte GmbH in Germany performed a genotoxicity test<sup>9)</sup> (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<sup>1)</sup>. 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<sup>10)</sup> 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%
- e) 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

### Clinical Documentation

#### **Saline infusion versus gel instillation sonography: a prospective cohort study<sup>11)</sup>**

*E. Werbrouck<sup>1</sup>, T. Van den Bosch<sup>1</sup>, J. Veldman<sup>1</sup>, J. Luts<sup>2</sup>, S. Van Huffel<sup>2</sup>, D. Van Schoubroeck<sup>1</sup>, D. Timmerman<sup>1</sup>*

*<sup>1</sup>Obstetrics & Gynecology, University Hospitals K.U. Leuven, Leuven, Belgium; <sup>2</sup>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.

#### **Hysterosalpingo Foam Sonography (HyFoSy) or Hysterosalpingo Contrast Sonography (HyCoSy) with Foam<sup>12)</sup>**

*Mark Hans Emanuel MD PhD, Ineke Tromp MD and Julie Knieriem MD  
Ob/Gyn Spaarne Hospital Hoofddorp (Amsterdam) The Netherlands*

**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:

**The Diagnostic Accuracy of Gel Instillation Sonohysterography (GIS) Compared with Saline Infusion Sonohysterography (SIS); a Randomised Controlled Trial<sup>13)</sup>**

*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 53) 35 abnormalities were found; 31 (89%) were confirmed during hysteroscopy. In the SIS group (n 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.

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**de Smit Medical Systems Ltd**  
**118a Station Road**

**Yate Bristol BS37 4PQ**

**Tel: +44 (0)845 3454226**

**Fax: +44(0)845 3454227**

**Email: [sales@desmitmedical.com](mailto:sales@desmitmedical.com)**

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