Essure HyCoSy Ultrasound Grant Application

Can Contrast Infused Sonography Using Air Bubbles Replace Hysterosalpingogram as the Diagnostic Evaluation of Fallopian Tube Patency Following Hysteroscopic Sterilization Using Essure™?

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Hypothesis:

We hypothesize that performing saline infused sonography (SIS) with directed air bubbles for hysterosalpingo-contrast sonography (HyCoSy) is at least as equivalent or superior in evaluation of fallopian tube patency following hysteroscopic Essure™ tubal sterilization in those undergoing X-ray hysterosalpingography (HSG). We also hypothesize that performing HyCoSy with air bubbles is more cost-effective and less painful than HSG.

Objectives:

Currently, in the USA, Essure is approved by the Food and Drug Administration (FDA) for hysteroscopic sterilization (1). The effectiveness of permanent sterilization is 99.8%, with successful bilateral placement rate for each delivery system approximately 96.5% (1,2). Current FDA labeling for Essure requires an HSG 3 months after placement to confirm the proper coil position and tubal occlusion (1). However, HSG is not the ideal confirmatory test given the following inherent issues (3-5):

1. Exposure to ionizing radiation
2. Cost
3. Patient discomfort
4. Inconvenience
5. Poor inter-observer reproducibility
6. Variability in the technique
7. Tubal spasm potentially creating the false impression of proximal tubal occlusion

In fact, 30% of unintended pregnancies after hysteroscopic tubal occlusion placement have been attributed to misinterpretation of the HSG (6). Thus, our primary objective is to determine if HyCoSy with air bubbles is equivalent to HSG in the diagnosis of tubal patency in patients undergoing hysteroscopic sterilization using Essure™. Secondary objectives include 1) Pain assessment of each

procedure and 2) Cost analysis. To address these objectives we propose the following specific aims:

Primary Specific Aims:

1. To demonstrate an equivalent or superior evaluation of fallopian patency by HyCoSy using air-bubbles in comparison to HSG.

Secondary Specific Aims:

1. To compare pain scores in those undergoing SIS/HyCoSy to HSG in order to assess overall tolerability of SIS/HyCoSy.
2. To compare assessment of the uterine cavity using SIS air-bubble contrast using SIS-catheter in comparison to HSG.

Background and Significance:

Tubal disease accounts for 30 to 40% of all cases of infertility (7,8). The gold standard for tubal evaluation is laparoscopy with dye (chromopertubation). The standard non-operative method for evaluating pelvic anatomy has been the HSG (9-11). The HSG, however, requires exposure to ionizing radiation and the need for iodinated contrast material. Proper technique in performing an HSG is imperative since inadequate uterine distension may result in poor visualization or overzealous instillation may easily obscure uterine pathology or cause inadvertent tubal spasm suggesting pathology (4, 7-11). In contrast, the use of sonography combined with intrauterine saline instillation, termed SIS, has become routine for evaluation of intrauterine cavity pathology and has been shown to have similar predictive value to hysteroscopy (12-15).

A number of clinical trials have suggested SIS application in fallopian tube assessment for infertility (16-48). Contrast agents that have been described include the use of a suspension of galactose micro-particle granules (Echovist-200®), perflutren lipid microspheres (Definity®), and air bubbles to enhance contrast in the fallopian tubes (sonosalpingography-SSG or hysterosalpingo-contrast sonography-HyCoSy). Each has been reported to have similar diagnostic accuracy as HSG with iodinated contrast material (17-21). Furthermore, there are added advantages of minimizing risks (i.e. no ionizing radiation), better 3-dimensional imaging of the uterus and allowing for the evaluation of tubal and ovarian pathology during the same study. Disadvantages of its use include false positive results of tubal occlusion related to tubal spasm, difficulty assessing fallopian tubes with abnormal anatomy and interference of echogenicity from over-lying bowel. Additionally, only one tube can be visualized at a time, therefore it is possible to miss flow through the contralateral tube with initial injection.

Specifically, studies using Echovist-200 (developed for cardiac ultrasound) demonstrated 83% agreement with HyCoSy compared to laparoscopy, compared to a 76% agreement with HSG and laparoscopy (22,42, 49-52). The contrast material, however, is very expensive (>$500), obviating its routine use in the office setting. The use of perflutren lipid microspheres (Definity®) in cardiac imaging has allowed for stability of the contrast media (50-52). Recent studies using Definity® microspheres have been described for its use with HyCoSy to assess tubal occlusion after Essure Tubal Sterilization, which demonstrated 100% agreement with HSG in assessing tubal patency

and 82% agreement with respect to tubal occlusion. Moreover, patients preferred undergoing HyCoSy in the comfort of the gynecology office rather than the radiology department (50). As such, while Definity® appears to be a safe and effective contrast media for HyCoSy, however, this contrast is not FDA approved and further studies are needed to determine its diagnostic accuracy and reproducibility.

A substituted a mixture of saline and air for distending media has also been described (16, 40–43) where some vigorously shake a syringe of saline and air creating air bubbles immediately before infusion, while others have described filling a syringe with both air and saline and tilting the syringe with the intermittent infusion of air followed by saline in increments of 1–3 mL (38,39, 53-55). Positive and negative predictive values for air contrast HyCoSy appears to be similar to other contrast materials for both tubal patency and occlusion when compared to both laparoscopy and HSG (38,55). However, as air bubbles disappear quickly, tubal assessment is limited. This method has been shown to have excellent predictive value (80%–87%) when compared to laparoscopy.

Recently, an FDA approved device, Femvue ™ Saline-Air Device, creates and delivers a consistent alternating pattern of saline and filtered air as a continuous stream in a controlled fashion allowing for fallopian tube evaluation under ultrasound guidance (56). Our objective is to determine if saline infused sonogram (SIS)-HyCoSy with Femvue ™ Saline-Air Device is equivalent or superior to HSG in evaluation of fallopian tube occlusion in those undergoing HSG following Essure hysteroscopic tubal occlusion as Comparative studies to HSG, are lacking.

The advantages of HyCoSy revolve around its applicability in the office, its cost effectiveness and the avoidance of radiation exposure. Although shown to be a practical procedure with investigations yielding high accuracy results for both tubal patency and tubal occlusion, as mentioned previously, studies are still needed to evaluate this subject matter further. Minimal data exist directly comparing HSG versus HyCoSy with air bubble contrast media ss the confirmatory test for post hysteroscopic tubal occlusion. We propose to determine the predictive value and possible overall superiority of HyCoSy to HSG from a time effective and pain scale model.

Experimental Design:

Thirty-six women who are undergoing post-Essure tubal occlusion evaluation will be invited to participate in this study. Subjects will be recruited and screened from the practice of Wright State OB-GYN Physicians.

Inclusion Criteria

1. Documentation of normal PAP smear within one year prior to subject enrollment in study.
2. Written consent to this study must be given voluntarily.
3. Need for evaluation of tubal status for post-Essure tubal occlusion.
4. Negative urine pregnancy test.

Exclusion Criteria

1. Any prior endometrial ablation procedures or plans to undergo endometrial ablation procedures prior to the Essure confirmation test.
2. History of unresolved dysfunctional uterine bleeding (DUB).
3. History of a hysterectomy.
4. Current urogenital disease.
5. History of allergic response to IVP dye (exclusion for HSG).
6. Abnormal pap smear.
7. Positive urine pregnancy test.

Procedure

As part of their post-Essure Tubal occlusion assessment, both air bubble HyCoSy and HSG will be performed at the same visit. Patients will undergo air bubble HyCoSy first, performed in the office setting, followed by HSG, which will be performed in the radiologic suite Miami Valley Hospital. A Likert Pain Scale will be completed prior to testing and at completion of the study for each procedure (See below).

1. *Saline Infused Sonography (SIS):*

SIS will be performed either during the follicular phase of a spontaneous menstrual cycle or following a progestin withdrawal bleed. All patients will be asked to take NSAIDs one hour prior to the procedure. A 2-mm lumen SIS balloon catheter will be placed transcervically during a speculum examination, with the balloon distended in the lower uterine segment or cervical canal. Routine transvaginal sonography of the endometrium, myometrium, and adnexae will be initially performed, followed by instillation of 5-10ml of sterile saline through the catheter for uterine evaluation. Transvaginal sonographic images of the sagittal and coronal views of the pelvis will be recorded with still images and video.

2. *Hysterosalpingo-Contrast Sonography (Air Contrast HyCoSy):*

This will be a randomized prospective trial, where patient will be randomly allocated initially to either the Air Contrast HyCoSy or the Hysterosalpingogram. At least one hour between procedures will be required.

<u>Air-Contrast HyCoSy</u>

After completion of the SIS evaluation of the uterine cavity, Air Contrast HyCoSy contrast will then be performed through the same catheter under direct ultrasound visualization The FemVue™ Saline-Air Device will be used for the air contrast HyCoSy. It is an FDA approved diagnostic tool used with SIS to evaluate the intrauterine cavity. The device is applied to the SIS catheter so that when filled, is an alternating mixture of air and saline that will be infused into the uterine cavity acting as a contrast agent for HyCoSy.

If fallopian tube patency is indeterminate, the patient will be repositioned into a lateral position at approximately 45° in order to better visualize the fallopian tube as previously described (17). The SIS catheter will be removed at completion of the HyCoSy procedure. Each patient will complete a pain and comfort survey using a Likert Scale questionnaire prior to and following the SIS and HyCoSy procedure (See Below). After completion of this survey, the patient will be directed to the radiology suite for their HSG.

3. Hysterosalpingography (HSG):

Similarly, an H/S catheter will be placed transcervically during a speculum examination, with the balloon distended in the lower uterine segment or cervical canal. Isovue 250 (iodine containing radiopaque contrast agent) contrast material will be instilled through the lumen catheter for evaluation of the uterine cavity and for fallopian tubal patency under X-ray visualization. Instillation of contrast will be performed and tubal patency evaluated with X-ray.

If fallopian tube patency is indeterminate, the patient will be repositioned into a lateral position at approximately 45° in order to better visualize the fallopian tube (17). The H/S catheter will be removed at the completion of the HSG. Each patient will complete a pain and comfort survey using the Likert Scale questionnaire prior to and following the HSG procedure (See Below).

Women will be randomized to receive the study procedures in one of two orders. Half of the women will be assigned to receive the SIS-Air HyCoSy first, followed by the HSG while the remaining half of women will receive the HSG first, followed by the SIS-Air HyCoSy.

4. Likert Pain Scale (Appendix A)

5. Further Testing

If tubal patency is suspected, further diagnostic and treatment options will be discussed, per standard of care by their primary physician. Any further diagnostic and treatment data obtained after any other uterine and/or tubal evaluation including hysteroscopy or laparoscopy will be collected for comparison to SIS, HyCoSy, and HSG evaluation. A pain scale and time assessment of each diagnostic arm will be performed and all subsequent testing and treatment will be documented.

Radiologic Interpretation:

Each SIS, HyCoSy, and HSG will have printed still and video images recorded on CD for review of the diagnostic findings. Images will be labeled with a study number that is distinct for each procedure and de-identified of all patient data. A reproductive endocrinologist (SRL) and a

radiologist (TW) will review all images and video recordings and correlate study interpretation.

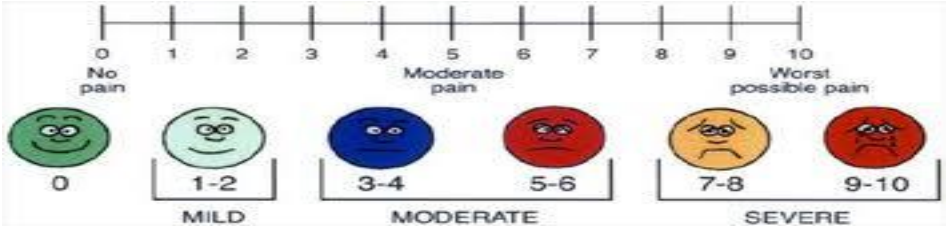
Compensation and Cost to Subject:

Subjects will be responsible for the Essure hysteroscopic sterilization. The study will cover all charges related to the cost of the SIS and HyCoSy and HSG. Subjects will be given $50 for their inconvenience and for participating in the study.

Statistics:

This will be a randomized prospective clinical trial, where patients will be randomly allocated to the Air Contrast HyCoSy or HSG initially followed by the other test with at least 1 hour between procedures. The primary outcome of interest is the agreement between the HSG and air-bubble HyCoSy in evaluating tubal patency. For this purpose the HSG will indicate either tubal patency or non-patency and will be considered as the gold standard, and the air-bubble HyCoSy will indicate either patency, non-patency, or inconclusive and compared to the gold standard HSG. Agreement between the evaluations will be measured using the kappa (κ) statistic. To detect a difference in kappa (a correlation) as small as 95% vs 99% you will need 36 with a 20% non-compliance rate. This means that you will be able to detect a difference as small as 95-99 OR anything larger. This translates into the assumption that even a 95% kappa is acceptable enough to call the methods 'the same.'

Appendix A. Likert Pain Score



	SIS-SSI	HSG
Consent		
Baseline Pain		
Pain with Balloon Placement		
SIS Findings		N/A
SIS Volume		N/A
Time to Complete SIS		N/A
Pain after SIS		N/A
SSI Findings		N/A
Time for SSI Completion		N/A
SSI Volume		N/A
Pain after SSI or HSG		
Cavity Findings on HSG	N/A	
Tube Findings on HSG	N/A	
HSG Volume	N/A	
Time for HSG	N/A	
Preferred Test		
Reasons:		

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Informed Consent

INFORMED CONSENT AND RESEARCH AUTHORIZATION

Can Contrast Infused Sonography Using Air Bubbles Replace Hysterosalpingogram as the Diagnostic Evaluation of Fallopian Tube Patency Following Hysteroscopic Sterilization Using EssureTM?

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Department of Obstetrics and Gynecology

Institution: Wright State University & Premier Health
Clinical Trials Research Alliance

Sponsor: Bayer Healthcare Investigator-Sponsored Grant Program

Site(s): Miami Valley Hospital

Phone number for subjects to call for questions: 937-208-2079

Introduction and Background Information

You have been asked to participate in a medical research study because you have had your tubes "tied" with the EssureTM device.

Purpose

The purpose of the study is to evaluate the use of air bubbles ("Air Contrast") and an ultrasound (hysterosalpingo-contrast sonography or "HyCoSy") as compared to the standard X-ray hysterosalpingography (HSG) in evaluation of tubal closure with EssureTM. HSG is an x-ray performed after injecting dye.

We aim to determine if HyCoSy with air bubbles is equal or superior to HSG as well as less painful than HSG. Neither one of these procedures is considered experimental.

A transvaginal ultrasound will be used in this study. It will be done as part of the procedure for infusing air bubbles into your uterus and fallopian tubes. The doctor will infuse saline into your uterus and fallopian tubes, then using the air bubbles device, he will infuse air into your fallopian tubes. He will use the ultrasound to watch the bubbles move through your fallopian tubes to see if your tubes are open.

Procedures

Your participation in this study will last for 1 day. If you consent to participate, you will have the

following procedures while you are in this study:

1. You will be asked to participate and sign this consent form.

2. The researchers will gather information about you either directly or by reviewing your medical records. This information will be used to decide if you are eligible for the study. The following information will be used and/or disclosed for this research study: age, BMI, number of pregnancies and treatment outcome data.

3. You will be asked to complete a Likert Pain Scale survey about your pain during each procedure.

4. You will be randomized (like the flip of a coin) to either undergo the SIS-Air-Contrast HyCoSy or HSG first followed by the other test within 1 to 2 hours. Subjects will be randomized to receive the study procedures in one of two orders. Half of the women will be assigned to receive the SIS-Air HyCoSy first, followed by the HSG while the remaining half of women will receive the HSG first, followed by the SIS-Air HyCoSy.

Air Contrast HyCoSy Group

For the ultrasound with air bubbles you will be asked to take over-the-counter pain reliever (such as ibuprofen) one hour prior to the procedure to minimize cramping. A speculum will be placed in the vagina, then a small catheter (smaller than a straw) will be inserted through the cervix and a small balloon inflated at the top of the cervix or lower portion of the uterus. The speculum will be removed and a transvaginal ultrasound probe with then be placed in the vagina. Through the catheter, sterile saline will be injected into the uterus to evaluate for any abnormalities within the uterine cavity. Ultrasound images will be recorded with images and video. After completing the evaluation of the uterine cavity, Air-Contrast HyCoSy will then be performed through the same catheter. A mixture of saline and filtered air will be introduced under direct ultrasound visualization using a FDA approved device called the FemVue™ Saline-Air Device. This mixture creates bubbles that can be seen with the ultrasound and will assess if the fallopian tubes are closed.

X-Ray HSG Group

For the x-ray HSG, again a speculum will also be placed in the vagina, then a similar small catheter will be inserted through the cervix and a small balloon inflated at the top of the cervix or lower portion of the uterus. Isovue 250 (iodine containing dye) will be injected and an X-ray will be taken to evaluate the uterine cavity and if the fallopian tubes are blocked. If the test is indeterminate, you will be repositioned to lie on your side.

Both Groups
If it is suspected that your fallopian tubes have not closed, your primary physician will discuss further testing and treatment. If you agree, any further testing or treatment data will be collected for comparison to the tests above.

Potential Risks

There are inherent risks associated with HSG, which will have been discussed with you by your doctor. Specific to this study, the air-contrast HyCoSy carries the risk of cramping, infection and bleeding. Risks will be minimized by using sterile technique and standard monitoring during the procedure.

There is a risk of loss of confidentiality. Replacing your name with a code and keeping the information on a secure server only accessibly to study personnel will minimize this risk. In addition, you may suffer harms that we have not seen before.

Benefits

There will be no direct benefit to you from participating in this study. However, it is hoped that the information gained from the study will help find an alternative to determine that a woman's tubes have been successfully "tied."

Alternatives

If you choose not to participate in this study, your HSG will be performed in the usual fashion.

Research Related Injury

If you are injured by being in this research study, the investigator will arrange for you to get medical treatment. Wright State University, the study site, nor the investigator has set aside money to pay for treatment of any injury. You and your insurance will be billed for the treatment of these injuries. Before you agree to take part in this research study you should find out whether your insurance will cover an injury in this kind of research. You should talk to the investigator or staff about this. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have a research related injury, please call Dr. Lindheim or Dr. Yaklic at 937-208-2079.

Compensation

You will be given a debit card with a MasterCard logo. The card will be loaded with $50 after the study visit is completed. This process takes approximately 24 hours, so you may not receive your payment immediately. You can also set up a PIN number with the card issuer so that you can use

the card at any ATM. However, please be aware that ATMs usually charge a fee to use their machine. In order for you to receive payment, Greenphire, the issuer of the ClinCard, will be provided with your social security number and other demographic information for tax related purposes.

Costs

The SIS-Air Contract HyCoSy and the HSG are being provided by the study. There will be no cost to you for participating in this study.

HIPAA Research Authorization

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides federal safeguards for your protected health information (PHI). Examples of PHI are your name, address, and birth date together with your health information. PHI may also include your medical history, results of health exams and lab tests, drugs taken and results of this research study. Your PHI may not be used or shared without your agreement, unless it meets one of the HIPAA exceptions.

State and federal privacy laws protect your health information. In most cases, health information that identifies you can be used or shared by the research team only if you give your permission by signing this form.

If you sign this form your health information will be used and shared to answer the research questions described above and to make sure that the research was done correctly. The time period when information can be used or shared ends when all activities related to this study are completed.

Your access to your health information will not be limited during this study.

You do not have to sign this form. If you do not sign this form you may not participate in the study and health information that identifies you will not be shared with the research team.

In our research, the research team will look at and may share information about you and your health. Federal law requires that health care providers and researchers protect the privacy and security of health information that identifies you. We may ask for your health information from your primary care physician.

Revocation of Research Authorization

You may cancel the permission you have given us to use and share your protected health information at any time. This means you can tell us to stop using and sharing your protected health information. If you cancel your permission:

- We will stop collecting information about you.
- You may not withdraw information that we had before you told us to stop.
  - We may already have used it or shared it.
  - We may need it to complete the research.
- Staff may ask your permission to follow-up with you if there is a medical reason to do so.

You may cancel your permission by writing to the investigator at the address on page one.

Information Available on ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Confidentiality

Total privacy cannot be guaranteed. We will protect your privacy to the extent permitted by law. If the results from this study are published, your name will not be made public. Once your information leaves our institution, we cannot promise that others will keep it private. Your information may be shared with the following:

- The sponsor, Bayer Healthcare
- The Wright State IRB and Office of Research and Sponsored Programs
- The local research team
- People responsible for billing, sending and receiving payments related to your participation in the study

- Greenphire, the issuer of the MasterCard for subject payment
- People who are responsible for research and HIPAA oversight at the institutions where the study is conducted
- Government agencies, such as:
  - Office for Human Research Protections (OHRP),
  - Food and Drug Administration, and
  - Office of Civil Rights

Data Security

Your name will be replaced with a code and kept on a secure server only accessibly to study

personnel.

Conflict of Interest

This study may involve a conflict of interest because the institution will be compensated for your participation in it through a grant provided by Bayer Healthcare. The institution will then pay the investigator for the research procedures he performs during your participation. Please ask the investigator how the institution and/or investigator will benefit by your participation in the study.

Voluntary Participation

Taking part in this study is completely voluntary. You may choose not to take part at all. If you decide not to be in this study, you won't be penalized or lose any benefits for which you qualify. If you decide to be in this study, you may change your mind and stop taking part at any time. If you decide to stop taking part, you won't be penalized or lose any benefits for which you qualify. You will be told about any new information learned during the study that could affect your decision to continue in the study.

Termination

The investigator, the IRB or the study sponsor has the right to stop this study at any point. The investigator may take you out of this study with or without your permission.

Participation in Other Research Studies

You may not take part in this study if you are currently in another research study. It is important to let the investigator know if you are in another research study.

Research Subject's Rights, Questions, Concerns, and Complaints

If you have any questions, concerns, or complaints about the research study you may contact Dr. Lindheim at 937-208-2079.

If you have any questions about your rights as a study subject, questions, concerns or complaints, you may call the Wright State IRB Office (937) 775-4462. You may discuss any questions about your rights as a subject with a member of the IRB or staff. The IRB is an independent committee composed of members of the University community, staff of the institutions, as well as lay members of the community not connected with these institutions. The IRB has reviewed this study.

Acknowledgment and Signatures

This form tells you what will happen during the study if you choose to take part. Your signature means that this study has been discussed with you, that your questions have been answered, and that you will take part in the study. This informed consent document is not a contract. You are not giving up any legal rights by signing this informed consent document. You will be given a signed copy of this consent to keep for your records.

_____
Printed Subject Name

_____ _____
Signature of Subject Date Signed

_____ _____
Signature of Person Obtaining Consent Date Signed