Official Title: Development of an Intrauterine Pressure Threshold to Confirm Tubal Occlusion

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1.3 Design and methodology

1.3.1 Research design and General Methodological Approach

In order to determine if intrauterine pressure can be used as a screening tool for confirmation of tubal occlusion after non-surgical permanent contraception (NSPC), we propose a study with two stages:

First stage: A cross-sectional, descriptive pilot study of intrauterine pressures taken in all consenting women presenting for hysterosalpingogram (HSG) for any indication over the course of twelve months. This will allow us to measure intrauterine pressure in a wide variety of women and to compare pressures in women with patent and occluded fallopian tubes. Additionally, we will evaluate the extent to which other factors are associated with intrauterine pressures such as BMI or parity. Using the above information, we will determine a threshold pressure to serve as a test with acceptably high sensitivity and specificity for diagnosing fallopian tube occlusion, using HSG as our gold-standard for comparison.

Second stage:
Recruitment for stage 1 was completed in December 2015 and unfortunately no significant difference in uterine pressure was found between women with patent and occluded tubes. However, there were many fewer women with occluded tubes recruited. Additionally, the majority of women with open tubes had not had prior term pregnancies whereas the majority of women with occluded tubes had undergone an Essure® procedure for permanent contraception after multiple term pregnancies. Maximum pressures for women with occluded and patent tubes were both averaged around 300mmHg. Given this novel information and the limitations of the recruited cohorts, the second phase will involve recruitment of parous women, 12 with a history of the Essure® procedure and 12 without. Intrauterine pressure will be measured as in stage 1, both with normal saline and again during HSG with contrast. A standard volume will be infused and drawn back to see if the amount of volume returned is associated with blocked or open tubes.

The study will be funded by the Society of Family Planning and coordinated through Oregon Health & Science University (OHSU) in Portland, Oregon. Study procedures will take place with Dr. Amy Thurmond at Women's Imaging & Intervention (WI&I) in Lake Oswego, Oregon. Study procedures will be initiated following approval of the protocol by the institutional review board at OHSU. All of the necessary data collection will be performed on the day of the procedure, minimizing loss to follow up of study subjects. Of note, Dr. Amy Thurmond is an experienced clinician-researcher and international expert in women's imaging. She is a former faculty member in radiology and adjunct professor in OB/GYN at OHSU, and she has an ongoing collaborative relationship with the OHSU OB/GYN Family Planning division. She has extensive experience as a PI. She has enrolled subjects for numerous studies at her imaging center and is familiar with good research practices.

1.3.2: Criteria for the selection of subjects

The WI&I center is a regional referral center for women's radiology. Women who need evaluation of their uterine cavity and fallopian tubes, either for infertility investigation or confirmation of tubal occlusion after Essure®, are referred to the center by their primary

gynecologist or fertility specialist. We will recruit separate cohorts for each stage. Inclusion and exclusion criteria will be the same for subjects in both Stage 1 and Stage 2.

Inclusion criteria:

1) Literate in English, Spanish, or Chinese
2) Ages 18-50
3) Already planning HSG as recommended by their referring physician
4) Able to understand and sign an IRB-approved informed consent form
5) Willing to complete a pre-procedure questionnaire

Exclusion criteria:

1) Currently pregnant as confirmed by positive high-sensitivity urine pregnancy test
2) Currently using an intrauterine device (IUD)
3) Hypersensitive to radio-opaque contrast
4) History recognized as clinically significant by the investigator, such as symptoms of untreated or recent pelvic infection

Inclusion criteria for Stage 2:

1) Literate in English, Spanish, or Chinese
2) Ages 18-50
3) No history of infertility with current regular menstrual cycles occurring every 24-37 days
4) At least one term vaginal delivery
5) Have a negative urine pregnancy test on day of HSG procedure and not be at risk of a luteal phase pregnancy
6) Willing to undergo a single HSG procedure
7) Able to understand and sign an IRB-approved informed consent form
8) Willing to complete a pre-procedure questionnaire

Exclusion criteria for Stage 2:

1) Currently pregnant as confirmed by positive high-sensitivity urine pregnancy test
2) Currently using an IUD
3) Hypersensitive to radio-opaque contrast
4) History of cesarean section
5) History recognized as clinically significant by the investigator, such as symptoms of untreated or recent pelvic infection

1.3.3 Subject recruitment and allocation

Subjects will be enrolled through Dr. Thurmond's WI&I Center. Patients meeting inclusion and exclusion criteria will be recruited for participation either when they call to make their appointment or when they arrive for their appointment. Schedulers and receptionists at the imaging center will be provided with a pre-scripted recruitment message (Appendix D). Patients

will be informed they will receive the same care whether or not they choose to participate in the study, and that they can remove themselves from the study at any point in time.

For Stage 2, participants will be recruited from both WI&I and the general population using IRB-approved advertisements and from regular visitors to family planning and other clinics serving reproductive-aged women for gynecologic care and reproductive health services. Previously enrolled Stage 1 subjects who have Essure® devices in place may be contacted to see if they would like to participate in Stage 2. Subjects will be selected for the study according to the selection criteria detailed above.

1.3.4 Description of the drugs and devices to be studied

We will use a small inline pressure sensor to continuously monitor pressure during the HSG procedure. The sensor is a single use sterile device (DPT-100 - Sterile Deltran Disposable Blood Pressure Transducer Box, Utah Medical, Midvale, UT). The device has a pressure sensor that is sealed and is compatible with inline fluid delivery through a Luer-Lock connector. The output cord connects to a pressure sensor (PressureMAT™, PendoTech, Princeton, NJ) for continuous monitoring and recording of pressure throughout the procedure. Use of the pressure sensor will not inherently change the HSG procedure so subjects will not be at any additional risk or undergo additional discomfort if they choose to enroll.

1.3.5 Admission procedure

Subject enrollment: Eligible patients will be offered information about the study when they call to schedule their HSG, check-in for their HSG procedure, or contact/are contacted by the Women's Health Research Unit (WHRU). If interested in participating, the potential subject will be mailed a copy of the study consent form to review prior to their scheduled appointment. On subject arrival for their HSG appointment, the study coordinator or investigator will verify that all inclusion criteria are met, review the study in greater detail, answer subject's questions, and obtain informed consent in English or using a translator for both the fully translated consent form for Spanish speaking patients or the short form for Chinese speaking patients. Study coordinators are employees of the WHRU at OHSU, have completed all required research training, and are familiar with the procedures of contraception-related research and use of the pressure monitor from an ongoing study.

Each subject will receive a unique study ID that will be recorded securely in a recruitment log. Following completion of informed consent, subjects will then fill out a questionnaire in the waiting room to obtain basic demographic data. The survey will be administered on a tablet computer using the online data management system RedCap or in paper form. Subjects will be weighed. Serum progesterone and estrogen levels will be obtained. Study coordinators are well trained in phlebotomy and will collect the samples to be run at the Oregon National Primate Research Center (ONPRC) laboratory.

Intrauterine pressure measurement and HSG procedure: An experienced board-certified radiologist will conduct the HSG using standard technique. A flexible 5 French balloon catheter will be introduced through the cervical os and inflated either in the endocervical canal or in the uterine cavity, using 1 cc of air. Iohexol 300mgI/ml (Omnipaque; or its equivalent) contrast media will be introduced using constant fluoroscopic guidance, and images exposed when the tube or tubes first start to fill, when contrast agent enters the peritoneal cavity, and to document any important finding. The contrast medium will be injected via an infusion pump set at a constant rate of 2-8 mL/min based on prior studies [11]. Usually 5 cc of contrast agent are used, up to a maximum of 20 cc of contrast, and 5 total films. Fluoroscopy time is 1.5 ± 0.7 minutes. Occasionally prone and/or 10 minute delayed images will be obtained in an attempt to completely visualize the fallopian tubes. We will use a small inline pressure sensor to continuously monitor pressure during the HSG procedure. The sensor is a single use sterile device (DPT-100 - Sterile Deltran Disposable Blood Pressure Transducer Box, Utah Medical, Midvale, UT) (Fig.1). The device has a pressure sensor that is sealed and is compatible with inline fluid delivery through a Luer-Lock connector. The output cord connects to a pressure sensor (PressureMAT™, PendoTech, Princeton, NJ) for continuous monitoring and recording of pressure throughout the procedure (Fig.2). Pressure will be measured continuously but we will mark the following points during HSG for uniform comparison of pressures during the procedure: 1. Catheter in place, balloon is filled; 2. Initial filling of cavity with contrast; 3. Initial filling of one tube; 4. Complete filling of both tubes; 5. End of filling; 6. Balloon deflated. We will mark the pressure at the time filling is discontinued if bilateral tubal occlusion is observed and also if the patient is repositioned during the procedure. Once the HSG procedure is complete, the radiologist will complete a brief survey indicating location of the catheter balloon on inflation, uterine position, results of the HSG and whether or not any uterine pathology or Müllerian anomalies were noted.

Figure 1. In line pressure sensor form Utah Medical

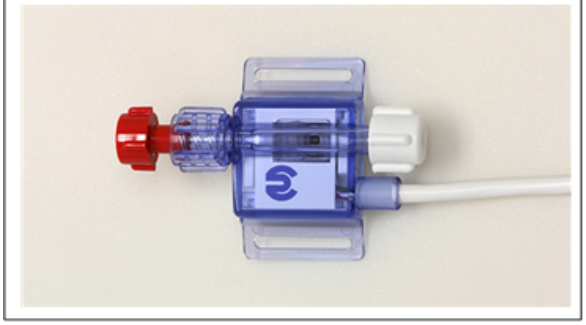
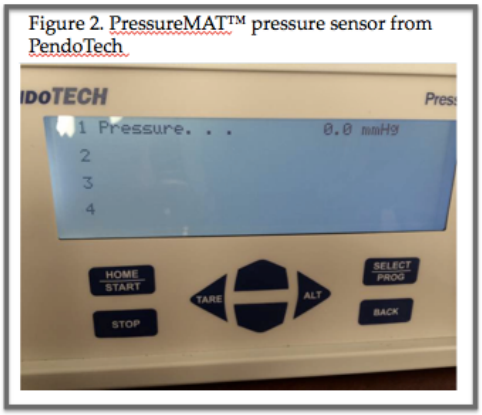


Figure 2. PressureMAT™ pressure sensor from PendoTech



Validation stage: In stage 2, the exact same enrollment, intrauterine pressure measurement and HSG procedure will take place in a second cohort of women. However, after the HSG catheter is placed but prior to contrast infusion, infusion of 10cc of normal saline via the HSG catheter and infusion pump will be performed. The infusion of saline will be done with the infusion pump at a constant rate as in stage 1, and will stop when a full 10cc has been infused or when the subject complains of pain or discomfort. After one minute, the radiologist will use the attached syringe to draw back the intrauterine fluid. This step has been added to both measure intrauterine pressure and the amount of fluid returned. This will provide information about the internal reliability of the pressure measurements as well as about the volume of fluid that can be recovered in patients with blocked or open tubes. Subjects will specifically be

recruited according to the above enrollment criteria to undergo the saline infusion, HSG and pressure monitoring procedure.

1.3.6 Follow-up procedure

All of the necessary data collection will be performed on the day of the procedure, minimizing loss to follow-up of study subjects.

1.3.7 Criteria for discontinuation

Patients have the right to withdraw from the trial at any time on their own request for any reason; the reason for withdrawal will be recorded in detail. No further data will be obtained from the patient once withdrawal occurs. If the HSG and intrauterine pressure readings have not been completed by the time of withdrawal, the subject will be excluded from analysis. The Data and Safety Monitoring will be conducted by the investigators listed on the first page of the protocol. They will meet on an as-needed basis if any serious adverse events related to the study protocol are reported by the investigator.

1.3.8 Laboratory and other investigations

A) Laboratory: Serum estrogen and progesterone levels will be collected at the radiology center, then transported and analyzed at the ONPRC endocrine core lab using a validated platform. Since many women have irregular cycles and may not be sure of menstrual cycle timing, serum hormone levels will confirm whether or not ovulation has occurred at the time of the HSG. The results of the blood draw will be entered into the RedCap data management system by a WHRU study coordinator. Since blood sampling may be a barrier to recruitment, the hormone samples will be optional for women with a history of regular cycles in the early follicular phase, However, all women with tubal occlusion will be asked to provide a blood sample.

B) Demographic and baseline clinical data: These will be self-reported and data will be collected on a RedCap computer-based questionnaire. We will ask information about age, height & weight, gravidity & parity, pregnancy outcomes, menstrual history including last menstrual period and menstrual history, current or recent contraceptive method if any, known uterine pathology such as fibroids, prior uterine procedures, surgeries, prior history of sexually transmitted infection, and known history of endometriosis or PID.

C) Intrauterine pressure measurements: These will be continuously collected and stored for each subject using the PressureMAT™ software (PendoTech, Princeton, NJ) on a password-protected laptop. The study coordinator will record the data points 1-6, time filling is discontinued if bilateral tubal occlusion is observed, and whether the patient is repositioned during the procedure in the PressureMAT™ software, as indicated by the radiologist during the procedure. Each subject's pressure data will be identified by their study ID and stored on the password-protected laptop.

D) Volume of media infused versus returned: A standard 10cc of saline and subsequently contrast will be infused until 10cc is in the uterus or until the patient complains of pain. After one minute, the radiologist will use the already attached syringe to draw back the fluid. The study coordinator will record the volume infused and the volume returned.

E) HSG results: The radiologist will complete a brief survey after each procedure on RedCap indicating location of the catheter balloon on inflation, uterine position, results of the HSG and whether or not any uterine pathology or Müllerian anomalies were noted. HSG images will be preserved as source documents for later review if needed.

1.3.9 Data management

The PI will manage data collection and monitoring for this study. Study personnel and study investigators will collect data at the procedure visit. The subject recruitment log will be kept confidential and in a locked office. A unique patient study identification number will be used for all RedCap data. Study identifiers kept in a logbook will be assigned to each patient to protect confidentiality. No patient names will be included with the study data during statistical analysis. Patient identifiers will be stored separately from the data files on the PI's password-protected computer. Only the study investigators will have access to this identifier list. Data and/or specimens from this study will be kept in a repository (WHRU Repository IRB # 6748) and may be shared using the patient study identification number with other investigators for future research.

1.3.10 Data analysis

The primary measurement for this study is the intrauterine pressure reading when filling is discontinued for subjects with tubal occlusion compared to the highest pressure obtained at data points 1-6 for those with tubal patency. We will refer to these measures as the peak intrauterine pressure. Secondary outcomes will include the correlation of subject characteristics with intrauterine pressures.

We will visualize data by plotting each subject's pressure reading trajectory across the six data points. We will characterize the mean, median and range of pressure readings at these data points. We will identify the peak intrauterine pressure for each subject to use as a continuous variable. A linear regression model will evaluate if other factors such as BMI, parity, uterine pathology or anomalies, or serum estrogen and progesterone levels are associated with peak intrauterine pressure. We will develop two-by-two tables to compare the various pressure thresholds to the gold-standard HSG findings and calculate the sensitivity and specificity of each pressure threshold. The sensitivities and specificities will then be used to create a ROC curve from which we will determine a pressure threshold value at which the area under the curve (AUC) is maximized.

Stage 1 revealed intrauterine maximum pressures averaging around 300mmHg for both subjects with patent and open fallopian tubes. Thus, 300mmHg will be considered the normal maximum intrauterine pressure and a clinically relevant increase in pressure for women with blocked tubes is considered an increase of 100mmHg. We will also measure the volume of fluid medium infused and recovered with the hypothesis that more volume will be recovered in subjects with blocked tubes compared to those with open tubes. A difference in volume of 3cc is estimated to be clinically relevant. We will recruit cohort of normally cycling parous subjects, half who have had Essure® procedures, and half who have not. The uterine pressures and the volumes of fluid instilled and recovered from the two cohorts will be analyzed in the same manner as Stage 1.

1.3.11 Number of subjects and statistical power

While this study is hypothesis-driven, an estimate of the effect size is not known. Therefore, the initial stage of the study will recruit patients already scheduled to undergo HSG for any indication to provide the basis for a follow up validation study with an appropriate sample size. The goal of the study will be to establish a "cut-off" pressure measurement at or above which fallopian tube patency is not observed. WI&I performed almost 300 HSGs last year, of which 90% were infertility evaluations and 10% were post-Essure confirmations. As we do not yet know the intrauterine pressure in patients with bilateral tubal occlusion, we will estimate pressures of less than 350 mmHg in women with bilaterally patent fallopian tubes [11]. Assuming 20% of the infertility population who come to clinic for HSG has blocked tubes based on WI&I estimates, and the 98% of success rate of Essure at 3 months, we can estimate the ratio of patent and blocked tubes as 72:28. Recruitment of 55 subjects would permit us to see a 300 mmHg elevation in those with occluded tubes with an alpha of 0.05 and power of 0.8 (Table 1). We anticipate an increase in 300 mmHg to be a conservative effect size estimate given abnormal (but not occluded tubes) have been reported to have a mean pressure over 800 mmHg [11]. However, in case the effect size is less than expected, we will enroll up to 150 subjects in stage 1; this would allow us to have sufficient power to exclude a 200 mmHg difference.

Table 1: Range of elevations in peak pressure that can be determined from a range of sample sizes

alpha	power	N	N1	N2	nratio	delta	m1	m2	sd
.05	.8	476	342	134	.39	100	350	450	393
.05	.8	121	87	34	.39	200	350	550	393
.05	.8	55	39	16	.39	300	350	650	393

Data from stage 1 were analyzed, but unfortunately a "cut off" pressure with maximal specificity and sensitivity was not identified. To address limitations of the stage 1 cohort, a second cohort of parous women will recruited to undergo pressure and volume measurements with a saline infusion and at the time of HSG. Given we have set a clinically significant change in pressure as 100mmHg above the average pressure for women with patent tubes (300mmHg, SD 80mmHg), 12 subjects (total N=24) will need to be recruited in both the Essure® and no-Essure® groups to achieve 80% power and an alpha of 0.05. This sample size will also allow us to detect a clinically significant difference of at least 3cc of fluid recovery between subjects with blocked and open fallopian tubes with an alpha of 0.05 and power > 80%. The needed number of subjects will be recruited from WI&I and WHRU.