Complete Title: Evaluation of Uterine Cavity Using Office Hysteroscopy Versus Saline Infusion Sonography: A Randomized Controlled Trial

Drug or Device Name(s): N/A

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PROTOCOL TITLE: Evaluation of Uterine Cavity Using Office Hysteroscopy Versus Saline Infusion Sonography: A Randomized Controlled Trial

Lead Investigator:

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Protocol Version:2.0

Version Date: June 10, 2019

I confirm that I have read this protocol and understand it.

Principal Investigator Name: Sarah Moustafa

Principal Investigator Signature: _____

Date: June 10, 2019

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
SIS	Saline infusion sonography
HSG	Hysterosalpingogram
OR	Operating room
PMH	Past medical history
PSH	Past surgical history
IVF	In Vitro Fertilization

PROTOCOL SYNOPSIS

Study Title	Evaluation of uterine cavity using office hysteroscopy versus saline infusion sonography: A randomized control trial
Funder	N/A
Clinical Phase	N/A
Study Rationale	Saline infusion sonography (SIS) and hysteroscopy are commonly employed methods for uterine cavity evaluation. SIS is often performed as a screening tool in the office for uterine evaluation since it is straight-forward to perform, well-tolerated has low overhead cost. If uterine pathology is suspected on SIS, subsequent hysteroscopy is typically performed in the operating room. Hysteroscopy remains the gold standard for diagnosis of intra-uterine pathology and offers the opportunity for intervention at time of diagnosis, but often is not used as the initial screening tool because of provider concerns about in-office tolerability, equipment cost and maintenance. Technology advancements, however, has introduced affordable, disposable, small caliber hysteroscopes with an operative channel to make it possible for this type of assessment to be performed in the office setting with the addition of a 'see and treat' modality. If used to perform initial uterine cavity evaluation, hysteroscopy may offer expedited diagnosis, treatment, and avoidance of general anesthesia. If superior specificity is demonstrated, it may also lower the false positive rate, preventing unnecessary delays to a patient's projected treatment plan, and unnecessary exposure to anesthesia risks. To date, no randomized control trials have compared the satisfaction of patients and providers to saline infusion sonography versus office hysteroscopy without anesthesia in initial cavity evaluation with the ability to immediately address intra-uterine pathology.
Study Objective(s)	1. Compare provider and patient satisfaction between SIS and office hysteroscopy 2. Report on capability of office hysteroscopy to adequately treat uterine pathology and avoid operating room management 3. Report on incidence of delay of fertility treatment in each group
Test Article(s) *(If Applicable)*	N/A
Study Design	This is a randomized control trial. Patients will be identified at time of their decision to undergo in-vitro fertilization, as all patients with this treatment plan undergo a cavity evaluation prior to initiation of fertility treatment. After obtaining informed consent, patients will be randomized to either the control arm with traditional SIS, or the intervention arm, using office hysteroscopy. Blocked randomization will be incorporated.

	Patients who demonstrate pathology on SIS will be scheduled for operative hysteroscopy in the operating room at a later date as soon as can be scheduled. Patients who demonstrate pathology including polyps or mild adhesive disease on office hysteroscopy will have attempted intervention at the time of initial procedure and/or will be taken to the OR with failure to complete the desired intervention or if significant pathology is encountered (myomas, severe adhesive disease). Patient and provider satisfaction will be assessed though questionnaires administered after each procedure. A statistical comparison of patients requiring subsequent procedure in the operating room in each group will also be assessed on intention to treat basis.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria 1. Women aged 18 – 50 2. Patients undergoing routine cavity evaluation for planned in vitro-fertilization cycles Exclusion Criteria 1. Clinical or radiologic suspicion of intrauterine pathology including myomas, severe intrauterine adhesions or retained products of conception 2. Those with medical criteria not suitable office hysteroscopy due to requirement of advanced tools or preparation not available in the office such as history of bleeding disorder or medical co-morbidity 3. Pregnancy
Number of Subjects	60 subjects. Power analysis requires a minimum of 25 in each group to detect a large effect size difference in satisfaction rate. An additional 5 subjects in each group, for a total of 30, to account for up to 20% drop out rate.
Study Duration	Each subject's participation will last for the duration of their uterine cavity evaluation and treatment of any pathologic findings and subsequent questionnaire. Recruitment is expected to last for one year with the entire study expected to last two years.
Study Phases Screening Study Treatment Follow-Up	(1) Screening: screening for eligibility and obtaining consent (2) Intervention: completion of either SIS or office hysteroscopy and (3) Follow up: post-procedure questionnaire, outcome of any subsequent surgical procedures
Efficacy Evaluations	Evaluation of satisfaction scores, ability to complete diagnostic and therapeutic goals, and time to fertility treatment

Safety Evaluations	All complications related to both study arms will be recorded, including pain, inability to complete procedure, bleeding, infection, or injury to the female reproductive tract.
Statistical and Analytic Plan	2 sample t- test will be used to compare mean questionnaire scores and delay in treatment comparison will be compared with chi squared tests. If significant differences exist in demographic features between groups, logistic regression will be performed to account for these. Dr. Patounakis will assist with statistical analysis. This is explained in further detail in section 6.
DATA AND SAFETY MONITORING PLAN	The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator is willing to provide access to her original records to permit verification of proper entry of data. At the completion of the study, any and all manuscripts will be reviewed by the Principal Investigator and will require her final signature to verify the accuracy of the data. The PI will monitor and evaluate the safety of the subjects throughout the course of the research study, by way of regular (every 6 months) meetings. If adverse effects are appreciated during an office hysteroscopy, the hysteroscopy will be stopped immediately, any medical concerns addressed appropriately, and alternate plans made for uterine cavity evaluation made. Confidential information will be protected by maintaining records in a secure, locked facility and deidentified files. Only those persons directly involved with the protocol will have access to personal health information. Data will only be presented and published in aggregate form with no personal identifiers. Our research group has been trained in human subjects' protection and only trained project staff operating under the IRB approval for the project will have access to the confidential individually identifiable data, and all data will be aggregated or anonymized for publication.
STUDY TEAM	Sarah Moustafa, MD, Principal Investigator (UNC) Linnea Goodman, Factulty Advisor (UNC) George Patounakis, MD, PhD, Biostatistician, (RMA Florida)

1.BACKGROUND AND RATIONALE

1.1 Introduction

Saline infusion sonography (SIS) and hysteroscopy are commonly employed methods for uterine cavity evaluation. SIS is often performed as a screening tool in the office for uterine evaluation since it is straight-forward to perform, well-tolerated has low overhead cost. If uterine pathology is suspected on SIS, subsequent hysteroscopy is typically performed in the operating room. Hysteroscopy remains the gold standard for diagnosis of intra-uterine pathology and offers the opportunity for intervention at time of diagnosis, but often is not used as the initial screening tool because of provider concerns about in-office tolerability, equipment cost and maintenance. Technology advancements, however, has introduced an affordable, disposable, small caliber hysteroscopes with an operative channel to make it possible for this type of assessment to be performed in the office setting with the addition of a 'see and treat' modality. If used to perform initial uterine cavity evaluation, hysteroscopy may offer expedited diagnosis, treatment, and avoidance of general anesthesia. If superior specificity is demonstrated, it may also lower the false positive rate, preventing unnecessary delays to a patient's projected treatment plan, and unnecessary exposure to anesthesia risks. To date, no randomized control trials have compared the satisfaction of patients and providers with the infertility workup experience when utilizing a single step process for evaluation and treatment (office hysteroscopy), as opposed to a two-step process, with separate procedures scheduled to diagnosis and then treat if indicated. The evaluation and management of infertility is often a stressful and time intensive process, often requiring delays in testing and intervention to coordinate with menstrual cycle timing. Therefore, in promoting a patient-centered experience, it may be beneficial to minimize steps proceeding ultimate treatment goals, such as in vitro fertilization.

The LiNA OperaScope is an FDA approved disposable 4.2mm office hysteroscope with an operative channel that allows for a 'see and treat' office modality for minor to moderate pathology such as polyps and minor adhesions without anesthesia. The device became available on the market in August 2018, and its use was immediately implemented in our clinic, as well as across the country. The device functions as standard office hysteroscopes before it, with the addition of an operative port, and all providers in this study are proficient in its use and have utilized it prior to the study start.

1.2 Name and Description of Investigational Product or Intervention

As previously noted, this device is no longer considered investigational, and is proficiently and regularly used in our practice and nationally.

1.3 Non-Clinical and Clinical Study Findings

Potential benefits the intervention arm of this study is fewer false positives, given direct visualization of the uterine cavity, and the ability to manage pathology at time of diagnosis. This may offer significant impact to the patient by avoiding anesthesia and a procedure in the operating room with associated burdens. It is likely also to significantly shorten time to planned treatment goals, which in our population of patient is conception/pregnancy.

1.4 Relevant Literature and Data

Saline infusion sonography is routinely employed method of evaluation for uterine cavity abnormalities. Studies have shown a sensitivity of 83% and specificity of 60%[1] for the detection of any pathology with SIS. Escalation to operating-room based hysteroscopy for further evaluation of intra-uterine pathology in the context of low specificity, leads to high number of unnecessary procedures under general anesthesia. This often results in unnecessary delays to treatment, and undue stress and inconvenience to the patient.

Hysteroscopy is regarded as the gold standard for uterine cavity evaluation with sensitivity of 97% and specificity of 92%[2]. While inherent risk of hysteroscopy is <1%[3], the use of general anesthesia results in additional morbidity risks[4], delays of primary treatment goals, and the occupation of many additional resources and personnel.

Office hysteroscopy has offered a distinct opportunity to avoid these additional risks, and a streamlined approach for patients and providers to complete evaluations efficiently. Patient satisfaction scores have been similar between office based and operating room base hysteroscopy, while recovery time and time away from work or home is significantly shorter in the former[5]. Operative office hysteroscopy for polypectomy and lysis intrauterine synechiae has proven a safe, effective, and cost-effective alternative to operating-room based hysteroscopy[6,7,8].

The goal of this study is to evaluate if office hysteroscopy is superior to SIS in a routine cavity evaluation prior to in-vitro fertilization.

2 STUDY OBJECTIVE

The objective of this study is to compare patient and provider satisfaction with office hysteroscopy (study arm) versus saline infusion sonography (control arm) for uterine cavity evaluation, and to compare time to infertility treatment.

The hypotheses are as follows:

1) Satisfaction: Providers will experience heightened satisfaction scores overall with the ability to more accurately visualize the uterine cavity, patients will have equal pain scores between modalities and both patients and providers will have overall increased satisfaction due to a complete assessment and treatment when indicated, expediting the ultimate care goals.

2) Time to infertility treatment: Patients in the study arm will encounter shorter times to desired treatment as they will be able to have pathology treated at time of diagnosis.

3) Providers will be able to complete cavity assessment and treatment of encountered pathology the majority of time that it is encountered with office hysteroscopy.

2.1 Primary Objective

1. Compare provider and patient satisfaction between SIS and office hysteroscopy
2. Report on capability of office hysteroscopy to adequately treat uterine pathology and avoid operating room management
3. Report on incidence of delay of fertility treatment in each group

2.2 Secondary Objective

Aim 2. Characterize and compare methods **SIS** and **office hysteroscopy** in terms of the proportion of patients with either incomplete cavity imaging or pathology noted requiring intervention in the operating room and evaluate time to initiation of desired fertility treatment.

3 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

Type of design: Randomized Control Trial

3.2 Allocation to Treatment Groups and Blinding (if applicable)

Uterine cavity evaluation is a routine step prior to initiation of in-vitro fertilization (IVF) treatment. When a patient has chosen IVF as their treatment plan, she will be assessed for eligibility in the study. If she meets criteria, the study information will be discussed, and written material provided. They will be counseled on risks and benefits of each arm before consent for randomization and will have adequate time (approximately two weeks) to review, ask questions, or withdraw prior to the procedure. Following recruitment and informed consent, subjects will be randomized to control (SIS) or study (office hysteroscopy).

When a patient is enrolled, an opaque envelope containing "control arm" or "study arm" will be opened to determine which arm the patient will be enrolled. The opaque envelopes will not be prepared by the study members executing the procedures and will be prepared in accordance to a block randomization scheme outlined by www.Randomization.com, in order to account for changes in skill and technique over time. Only 2 providers, both with experience using the LiNa Operascope will perform the hysteroscopies in the study. Due to the nature of the procedure, blinding for subjects or investigators would not be possible. At time of statistical analysis, the investigator performing analysis will be blinded from the group from which data was obtained.

3.3 Study Duration, Enrollment and Number of Subjects

Each subject's participation will last for the duration of their uterine cavity evaluation, subsequent questionnaire and they will be followed until there is resolution of any pathology encountered for final outcomes. Recruitment is expected to last for one year with the entire study expected to last two years. We plan to enroll a minimum of 60 subjects.

3.4 Study Population

Patients will be consecutively recruited at a single academic IVF program.

Inclusion Criteria: Subjects aged 18 – 50 years and undergoing routine cavity evaluation for in vitro-fertilization treatment cycles.

Exclusion Criteria: Clinical or radiologic suspicion of severe pathology including myomas, intrauterine adhesions or retained products of conception, and those with medical criteria not suitable office hysteroscopy due to the anticipated requirement of more advanced resources available in the hospital setting only such as history of a bleeding disorder or other medical co-morbidities.

4 STUDY PROCEDURES

4.1 Screening/Baseline Visit procedures

At time of recruitment, the following patient information will be obtained (or reviewed, if collected in prior visits): Age (years), BMI (kg/m^2), demographic variables (race, ethnicity) , gravidity/parity, PMH, and PSH.

4.2 Intervention/Treatment procedures

All procedures will be scheduled in the first ten days of menstrual cycle, in order to avoid possibility of pregnancy. If patient has irregular cycles, a urine pregnancy test will be performed and confirmed negative prior to procedure.

Patients randomized to the control arm will have standard cavity evaluation with SIS. This is performed by placement of speculum, prepping the cervix with betadine, placement of small flexible catheter, instillation of normal saline while recording images of fluid-distended cavity. Those with identified pathology will undergo typical management of our practice which includes: If imaging is unclear or equivocal, they may be offered repeat SIS and/or if SIS clearly depicts a suspected pathology, the patients will undergo operative hysteroscopy in the operating room at the next available date.

Those randomized to the intervention arm will undergo hysteroscopy with one of the study investigators, all of whom are fully trained and have privileges to perform hysteroscopy at UNC. A speculum will be placed, the cervix will be prepped with betadine, and the hysteroscope introduced. Hydro-distension will be accomplished using normal saline using gravity. Pictures of the uterine cavity will be obtained. If pathology (polyps or mild adhesions are visualized, the associated hysteroscopic graspers will be introduced through the operative port and used to attempt therapeutic intervention on visualized pathology, by utilization of graspers to remove polyps or adhesions. Results of the procedure will be recorded, and specimens sent for pathology evaluation as indicated. If efforts to introduce the hysteroscopy through the cervix are unsuccessful or if we are unable to remove an identified intrauterine pathology or patient discomfort is too high (as defined by the patient), the procedure will be aborted and the patient scheduled for intervention in the operating room at UNC, as is standard. No local analgesia will be used (as is standard practice in our office), but patients will be encouraged to take ibuprofen at home as is standard. They will be counseled to do this prior to SIS as well.

If uterine cavity visualization is unable to be completed with hysteroscopy for any reason, an SIS will be performed. Patients will be assessed according to intention to treat. Therefore, patients randomized to hysteroscopy and ultimately require an SIS will be considered a failure of hysteroscopy to appropriately visualize the uterine cavity, and the SIS will not be considered in the final evaluation as it was not the intended arm for that patient.

The outcome of the subsequent operating room operative hysteroscopies will be recorded to evaluate the positive predictive value of both groups.

We will record findings of both imaging modalities for each patient, so that subgroup analysis on patient satisfaction based on pathology identified may be performed if indicated.

The research site is a facility which routinely performs office hysteroscopy, SIS, dilation and curettage, egg retrievals, embryo transfers, uterine biopsies, and pelvic ultrasounds. It has a fully equipped OR to manage these procedures. Patients who are deemed high risk medically according to the exclusion criteria will not be enrolled in the study, as our OR is not equipped to manage serious adverse events (which are not anticipated as a risk in this procedure). All nursing staff in our facility has already been trained on how to assist with office hysteroscopy.

4.3 Follow- up procedures

As is standard for our clinic, if there is concern for pathology in the control arm, the patient will either undergo repeat SIS or hysteroscopy in the operating room, at the provider's discretion. Patient in the study arm will be

sent to the operating room if an intervention is required and unable to be completed at time of initial evaluation (hysteroscopy). Once a patient is routed to the operating room for management, outcomes will be reported.

Patient and provider questionnaires will be administered after the completion of SIS or in-office hysteroscopy. Since there will be no use of medication to alter consciousness, it is expected that patients will be in appropriate condition to complete a questionnaire after their procedure.

4.4 Unscheduled visits

The PI will be notified of any visits that occur as a direct result of the office hysteroscopy. Patients will be accommodated as soon as possible, and there is a physician available 24 hours/day for emergencies. Any non-routine visits, calls, or concerns that result from the either arm of the study will be recorded.

4.5 Concomitant Medication documentation

Not applicable

4.6 Subject Completion/ Withdrawal procedures

A patient may withdraw at any time by contacting the UNC Fertility office to indicate their desire to do so. They will also be asked on the day of the procedure if they still wish to participate in the study prior to beginning. It will be the personal responsibility of the PI to dispose of any associated data collected to that time point appropriately.

4.7 Screen failure procedures

Patients who do not qualify for the study will undergo standard evaluation and treatment by our clinic.

5 STUDY EVALUATIONS AND MEASUREMENTS

At time of recruitment, the following patient information will be obtained (or reviewed, if collected in prior visits): Age, BMI, demographic variables, indication for cavity evaluation, gravidity/parity, PMH, and PSH. Patients in intervention arm would not be subjected to additional exams or medical investigation than those in the control arm.

Satisfaction scores will be calculated from a standardized questionnaire utilizing a rating scale from 6-30 (see appendix) for patients and providers.

5.1 Efficacy Evaluation

Efficacy will be calculated based on ability to obtain satisfactory uterine cavity imaging by providers, as defined by the provider, and satisfaction of procedure experience by the patient. Mean satisfaction scores will be calculated and compared.

For the secondary endpoint, efficacy will be calculated based on proportion of patients with either incomplete cavity imaging or pathology noted requiring intervention in the operating room. Time to treatment will be compared with those with normal findings on either method uterine evaluation and those with pathology successfully removed in the study arm at time of diagnosis defined as 0 (or immediate), those with findings requiring operative intervention using days to scheduled OR visit as a continuous variable.

The number of patients with pathology requiring intervention noted will be recorded for each group. If this is significantly different between groups, logistic regression will be performed to control for this difference.

5.2 Safety Evaluations

Potential risks of office hysteroscopy include bleeding, infection, pain, uterine perforation, or inability to complete the procedure. Significant bleeding or infection is exceedingly rare with hysteroscopy. If significant discomfort is encountered, the procedure will be aborted. In our practice, this occurs at similar rates between these two procedures, which is less than 5% of procedures.

All procedures will be performed with standard methods, and any complications or adverse effects or concerns will be recorded and reported. The risk associated with hysteroscopy is <1%[3]. Adverse events will be recorded by study members as they are reported by participants. All adverse events occurring during the study will be documented, and reported to the faculty advisor, who will be available either on-site or via cell phone to discuss any safety issues that arise. The occurrence of adverse events will be assessed during the study and the faculty advisor will follow all adverse events to the point of satisfactory resolution. Immediate and appropriate medical care will be provided as indicated, and study personnel are experienced and qualified in managing complications of uterine imaging procedures.

The rate of adverse events between each group will also be recorded.

6 STATISTICAL CONSIDERATION

6.1 Primary Endpoint

Satisfaction scores of patients and providers

6.2 Secondary Endpoint

Time to infertility treatment, ability to successfully manage intrauterine pathology at time of diagnosis in study arm, positive predictive value of SIS in control arm

6.3 Statistical Methods

Dr. George Patounakis, with whom the faculty advisor has worked extensively for biostatistical analysis and will be added as a full investigator in order to assist and oversee statistical analysis. He has had an opportunity to review the protocol and will continue to offer guidance and expertise throughout the study.

Patient demographics variables, as previously defined, will be recorded and compared between groups using t-test for continuous parametric variables (mean age, BMI) and chi squared (race, parity). If differences are found, regression models will be used to account for those differences.

Satisfaction scores will be calculated based on ability to obtain satisfactory uterine cavity imaging by providers and satisfaction of procedure experience by patient, as defined by the rating scale in the questionnaires. The combination of multiple Likert scale responses from a single subject's survey response will be used as the satisfaction score. Combining the multiple ordinal variables from a single survey to obtain the score for that participant's response increases the likelihood of the satisfaction score behaving like a normally distributed variable so parametric statistical tests can be used. Prior to applying the parametric statistical tests to the satisfaction scores, the distribution of the scores will be assessed for normality. If the data is approximately normally distributed, then mean scores will be calculated in each group, and t-test used to compare these values.

Since this study has two primary endpoints, patient satisfaction score and provider satisfaction score, multiplicity will be addressed. To control for the inflated Type I error in this study, the Bonferroni correction will

be applied to the statistical test thresholds to assure an overall Type I error rate for the primary outcomes is less than 0.05.

For the secondary endpoint, time to initiation of fertility treatment will be evaluated as immediate (0) if: no pathology is encountered in either group or pathology is encountered and successfully treated in the hysteroscopy group. Time to initiation of treatment will be assessed as delayed by way of a continuous variable of days to scheduled repeat SIS or operating room surgery, if either method is inconclusive or pathology is encountered in either group that necessitates additional operating room management. The time to conceive will then be compared using medians with interquartile ranges and a Mann Whitney-U test for the non-parametric continuous variable of time and using chi-squared to asses the bivariate questions of immediate vs. delayed.

There should be minimal missing variables or dropout once the patients have started cavity evaluation for the primary outcome of patient and provider satisfaction unless there are areas left blank on the surveys. If areas are left blank, the patients will be asked by an investigator if this was in error or if they chose not to answer. If they chose not to answer, this will be noted. If patients fail to follow-up for subsequent operative management of pathology, time to treatment will be calculated as to the nearest available OR date that they would have been able to schedule.

The incidence of pathology between the two groups will be calculated and if this is significantly different, regression models will be applied to compare time to intervention while accounting for this. As all patients will be recruited from the same pool of those initiating IVF treatment, we hope to minimize selection bias. Results will be presented as adjusted mean differences or adjusted odds ratios as dictated by regression and dependent variable Dr. Patounakis, with significant experience in biostatistics, will assist and oversee statistical analysis. All hypothesis tests that are observed to be not statistically significant will be reported as being inconclusive.

The following established best practices will be followed: www.consort-statement.org and www.icmje.org.

6.4 Sample Size and Power

Accurate calculation of sample size is limited by lack of prior data for the standard deviation of satisfaction score responses. Therefore, for this study, an assumption will be made that the “effect size” is large and equal to 0.8. Sample size calculation for a power of 80% and alpha of 0.05 with large effect size of 0.8 for comparing means with a t-test indicates that approximately 25 subjects are needed in each group. We plan to enroll 60 patients, 30 in each group, to allow for approximately 20% patient dropout.

7 STUDY INTERVENTION

Office hysteroscopy will be performed in place of SIS for uterine cavity evaluation. Devices will be received directly from the manufacturer. Devices are in self-contained packaging, will be disposed of after one use with one patient.

8 STUDY INTERVENTION ADMINISTRATION

Administration of randomization and intervention when applicable will be performed only by co-investigators of this study. Opaque envelopes containing the treatment arm to which each subject will be randomized will be sealed and opened only at time of scheduling office procedure. The intervention will be performed only by study members previously trained with the device.

9 SAFETY MANAGEMENT

The Principal Investigator is responsible for personally overseeing the treatment of all study patients. A nurse or medical assistant will be present in all procedures, as is standard for our practice, to monitor patient safety and comfort. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. The Principal Investigator is willing to provide access to her original records to permit verification of proper entry of data. At the completion of the study, any and all manuscripts will be reviewed by the Principal Investigator and will require her final signature to verify the accuracy of the data.

Adverse Events: All adverse events occurring during the study will be documented (for up to 30 days following the procedure), and reported to the faculty advisor, who will be available either on-site or via cell phone to discuss any safety issues that arise. The occurrence of adverse events will be assessed during the study and the faculty advisor will follow all adverse events to the point of satisfactory resolution. Immediate and appropriate medical care will be provided as indicated, and study personnel are experienced and qualified in managing complications of uterine imaging procedures. Dr. Moustafa and Dr. Goodman will review any reported adverse events with the study team every 6 months.

10.1 Monitoring Plan

Adverse events that are possible include bleeding, infection, or injury to the female reproductive tract. Hysteroscopy is considered a low-risk office procedure, and none of these events are anticipated. However, all patients will be assessed for development of adverse effects during their visit and will have access to a trained Reproductive Endocrinologist and Infertility Specialist after their visit, who is on call 24 hours a day.

Serious Adverse Events
No serious adverse events are expected with the proposed intervention. If they should occur, they will be immediately reported.

Process of Reporting of Adverse Events:
The trial period is defined from the time that the informed consent document is signed until thirty days after the hysteroscopy. All serious adverse events occurring during this period (including death due to any cause) must be communicated within 1 day of the investigator becoming aware of the event to designated personnel. Any fatal or life-threatening adverse events must be reported immediately, but no longer than 1 day from the time the investigator becomes aware of the event. A causality assessment will be provided for all serious adverse events. Critical follow-up information on serious adverse events will be provided as soon as it is available, but no longer than 1 day from the time the investigator became aware of the information.

Reporting of Serious Adverse Events
Adverse events (non-serious) will be reported to the PI. The report will contain the details of the adverse event including temporality of event with study treatment, presentation, and follow-up plan. The clinician's rating of the severity of event/effect is recorded for each event. The rating will be based on the clinician's judgment of greatest severity of the adverse events. All serious events will be reported within 24 hours to the IRB.

10.2 Adherence to the Protocol

Except for an emergency in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.
The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.4 Record Retention

Study documentation includes all Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Study documents will be kept on file until three years after the completion and final study report of this investigational study.

10.5 Data Safety Monitoring Plan

The faculty advisor and PI will monitor and evaluate the safety of the subjects throughout the course of the research study, by way of regular (every 6 months) meetings with all study personnel in which they will review the following processes:
-Assess the performance of the trial with respect to subject recruitment, and data quality and completeness, to help ensure the likelihood of successful and timely trial completion.
-Review and consider any protocol modifications or ancillary studies proposed by the study investigators to ensure that these do not negatively impact the trial.
-Advise the Institutional Review Board as to whether the protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.

The PI will meet with study personnel at least twice per year to monitor the cumulative safety data during the period when participants are in the study.

10 DATA COLLECTION AND MANAGMENT

Maintenance of Confidentiality
Confidential information will be protected by maintaining records using RedCap. Only those persons directly involved with the protocol will have access to PHI. Data will only be presented and published in aggregate form with no personal identifiers.

Our research group has been trained in human subjects' protection and only trained project staff operating under the IRB approval for the project will have access to the confidential individually identifiable data, and all data will be aggregated or anonymized for publication.

The electronic data file linking patient MRNs to the patient-specific Study ID codes and group assignment will be password-protected file on the secure medical school-managed server with power surge protection and virus and malware intruder protection and accessible only to the PI and faculty advisor.

Deductive disclosure is protected against by lack of use of paper printouts, agreement to use data solely for statistical reporting and analysis, password protection of all health data, and the only copy of the patient MRNs will be in a secure and locked document as above.

Data integrity will be assured through prompt and comprehensive documentation of the procedure, complications, and outcomes, in our electronic medical record system, ArtWorks. This documentation will be completed by the physician executing the procedure. Any missing data queries will be conducted by the PI, who will also be responsible for analyzing data and creating the data dictionary.

Any study related data files and will be managed, processed, and stored in a secure environment (REDCap). Dr. Sarah Moustafa will be responsible for programming/computing for data management.

11 RECRUITMENT STRATEGY

Eligible subjects scheduled to undergo routine cavity evaluation prior to IVF treatment will be identified from the UNC Fertility schedule and recruited only by identified investigators. The investigator will inform the patient about the study and will invite her to participate. If interested, the rationale of the study and its methods will be described in detail and the patient consented.

12 CONSENT PROCESS

The investigator will identify eligible subjects and approach them either at the time of their scheduled appointment to discuss IVF, or at the time that uterine cavity evaluation is scheduled. This will take place on site at UNC fertility. All subjects will have the full study explained to them by the investigator and will have ample opportunities to ask questions prior to signing consent forms. Consent forms will be provided or emailed to patients prior to signing as needed to allow them longer time to review. Informed consent will be obtained from all patients prior to the performance of any study-related procedure or intervention. A copy of the signed consent form will be given to the subject and the original will be retained by research staff.

13 PLANS FOR PUBLICATION

The plan for this study includes presentation in abstract form at a national meeting and subsequent publication in a journal in the field of Reproductive Endocrinology and Infertility.

14 REFERENCES

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15 APPENDIX

Questionnaires to be used in the following 2 pages

PATIENT **Subject #:**

Date:

	Very unsatisfied (1)	Somewhat unsatisfied (2)	Neutral (3)	Somewhat satisfied (4)	Very satisfied (5)
Your overall procedure experience					
Ease of scheduling					
Pain control during the procedure					
The time it took to complete your procedure					
Understanding of the results of the procedure					
Satisfaction with follow-up plan of the procedure					

Pain rating on a scale of 1 -10 (1 being none, 10 being the worst pain you've ever experienced):_____

How likely are you to recommend this procedure to a friend (1 not at all, 10 extremely likely):_____

PROVIDER **Subject #:**

Date:

Indication:

Tool used:

- ☐ LiNA
  - Additional tools used (tenaculum ect):
- ☐ SIS
  - Tools used (balloon catheter, tenaculum etc):

Ability to complete procedure: Yes/No

Was there pathology visualized: Yes/No Suspected pathology: _____

Was the pathology able to be removed at the time: Yes/No

	Not at all satisfied (1)	Somewhat unsatisfied (2)	Neutral (3)	Somewhat satisfied (4)	Very satisfied (5)
Ease of scheduling					
Ability to complete the procedure					
Uterine cavity evaluation					
Ability to see and treat					
Perceived pain or patient experience					
The time it took to complete the procedure					
Overall satisfaction with the procedure					

Ease of use of tool on a scale of 1-10 (1 being extremely difficult and 10 being extremely easy):_____

Time to complete procedure: _____

Analgesia used:

Premedication (Tylenol, motrin, benzodiazapam, other): yes/no, specify_____

Staff involved:

Any issues:

Are additional procedures necessary? _____

If so what is the plan: _____ What is the next available date for this plan:_____