Training Overview for Track One and Two Participants

Before using the commercial Adiana Transcervical Sterilization System, all physicians will need to complete training and demonstrate understanding in:

- Screening and counseling patients for this device
- Discussing procedure warnings and precautions with the patient
- Successfully performing the Adiana Transcervical Sterilization Procedure in accordance with the FDA approved Instructions for Use
- Interpreting hysterosalpingograms and managing equivocal readings
- Managing challenging cases

Didactic and simulation training will be offered through web based training programs, classroom training, or in office training by Cytyc trained representatives. Procedures will be overseen, as appropriate to the tier of training and/or physician request, at the clinical facility and will be provided by Cytyc trained representatives.

All physicians who are enrolled in the Adiana Procedure will receive didactic and appropriate simulation training in the following topics (See Proposed Commercial Product Training Flowchart, Figure 6.2):

Adiana Transcervical Sterilization System

- Understand and Counsel Patients on the Adiana Procedure
  - Device Overview
  - Prior Studies and Clinical Trial Results
    - Device Safety Results (from final SS&E)
    - Device Effectiveness Results (from final SS&E)
  - Scheduling and counseling patients on the Adiana Procedure
  - Device Warnings and Precautions
  - Patient comfort during procedures
  - Patient follow-up requirements
- Performing the Adiana Procedure
  - Patient and Equipment set-up
  - Overview of principles of the Adiana Procedure
    - Tubal Access
    - Positioning and Stabilizing the Hysteroscope
    - Catheter Handling
    - PDA and Activation
    - Matrix Release
    - Post Procedure Management
- Managing Challenging Cases
  - Difficult Access
  - RF Treatment Challenges
- Case Simulation

2. Adiana HSG Procedure HSG Training

Performing and properly interpreting HSGs has been an important aspect of the Adiana Training Program for the EASE Clinical Trial and continues to be for commercialized product. To ensure that physicians who interpret HSGs for commercial product are successful, a separate training program has been developed. Designed for both gynecologists and radiologists, it will present information specific to performing the Adiana procedure, interpreting Adiana HSGs and managing challenging cases. A separate HSG Manual has been drafted. Examples of Confirmatory and Equivocal readings will be included and discussed.

Training in the following topics will be included (See Proposed Commercial Product Training Flowchart, Figure 6.2):

Adiana HSG Procedure

- HSG Procedure Overview
  - HSG Safety
  - Patient and Equipment set-up
  - HSG Procedure
    - Required images and interpretation
    - Confirmatory Interpretation
- Manage HSG Challenges
  - Equivocal Occlusion
  - Repeat Evaluation and Patient Management
  - Cytyc Clinical Support

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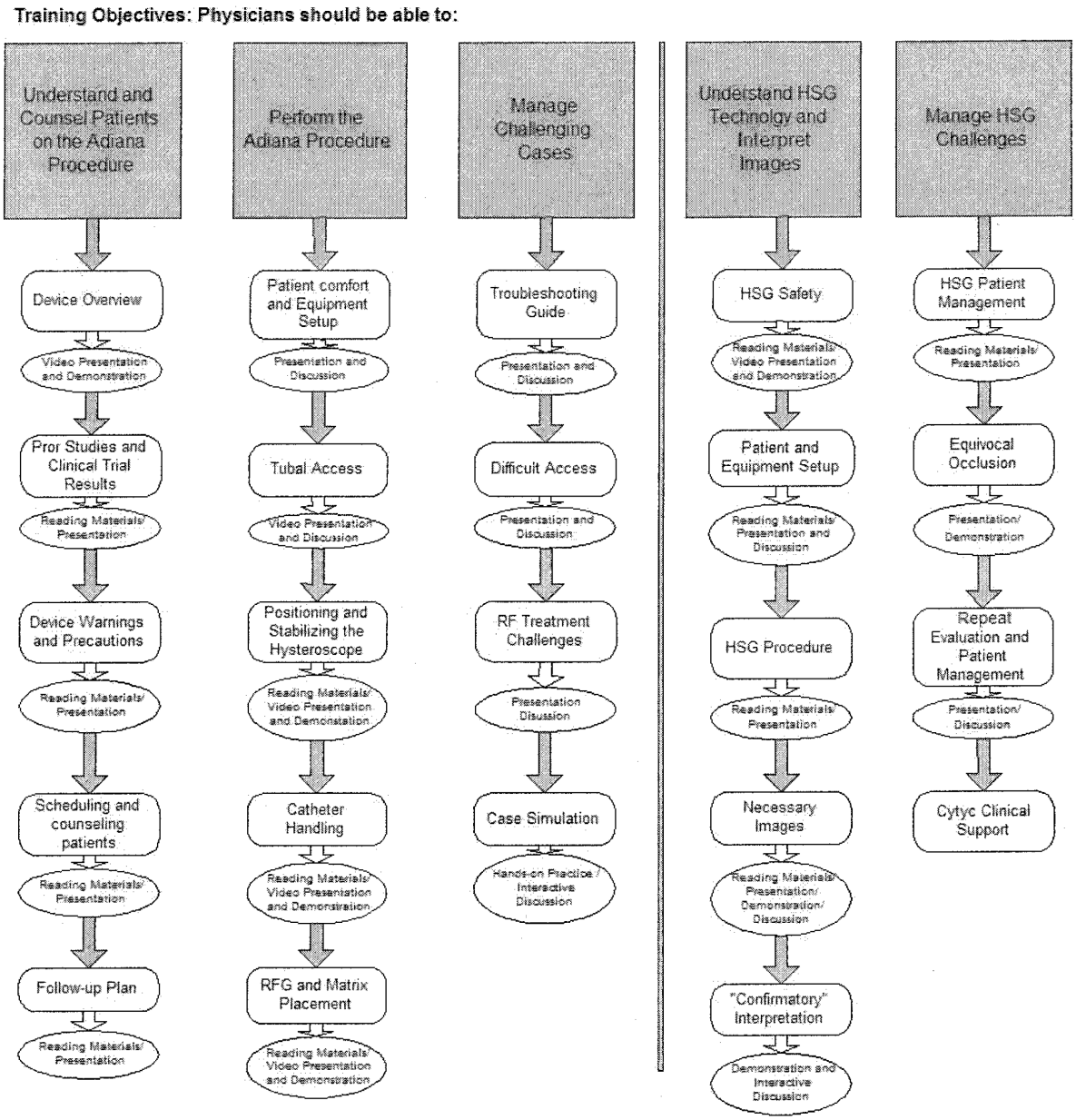
Figure 6.2: Proposed Commercial Product Training:



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VIII. B. TRAINING MANUALS

VIII. B. 1. PHYSICIAN TRAINING

Cytyc Surgical Products

Adiana Transcervical Sterilization System

System Usage Physician Training

Objectives

- Understanding and counseling patients on the Adiana procedure
- Performing the Procedure
- Managing Challenging Cases

Understanding and Counseling Patients on the Adiana Procedure

Product Safety

- Contraindications
- Warnings
- Precautions
- Adverse Events

(as presented in IFU and SS&E)

Patient Counseling

- This device does not provide sterilization protection for at least than 3 months, at which time tubal occlusion must be confirmed by HSG.
- Until HSG confirmation, patients must protect against pregnancy by utilizing an alternative birth control method.
- The alternative birth control method should be selected in advance of the treatment procedure.

Patient Counseling

The Adiana procedure is permanent and irreversible; alternative temporary methods are available.

Review of alternative birth control options

Patient Scheduling

- To reduce the possibility of a luteal phase pregnancy, the procedure should be performed during the early proliferative phase of the menstrual cycle.
- Device placement should NOT be performed during menstruation.
- A pregnancy test administered by the physician or designee should be conducted within 24 hours prior to the Adiana procedure.

Follow Up Plan

- 3 Month HSG
- Alternative Contraception

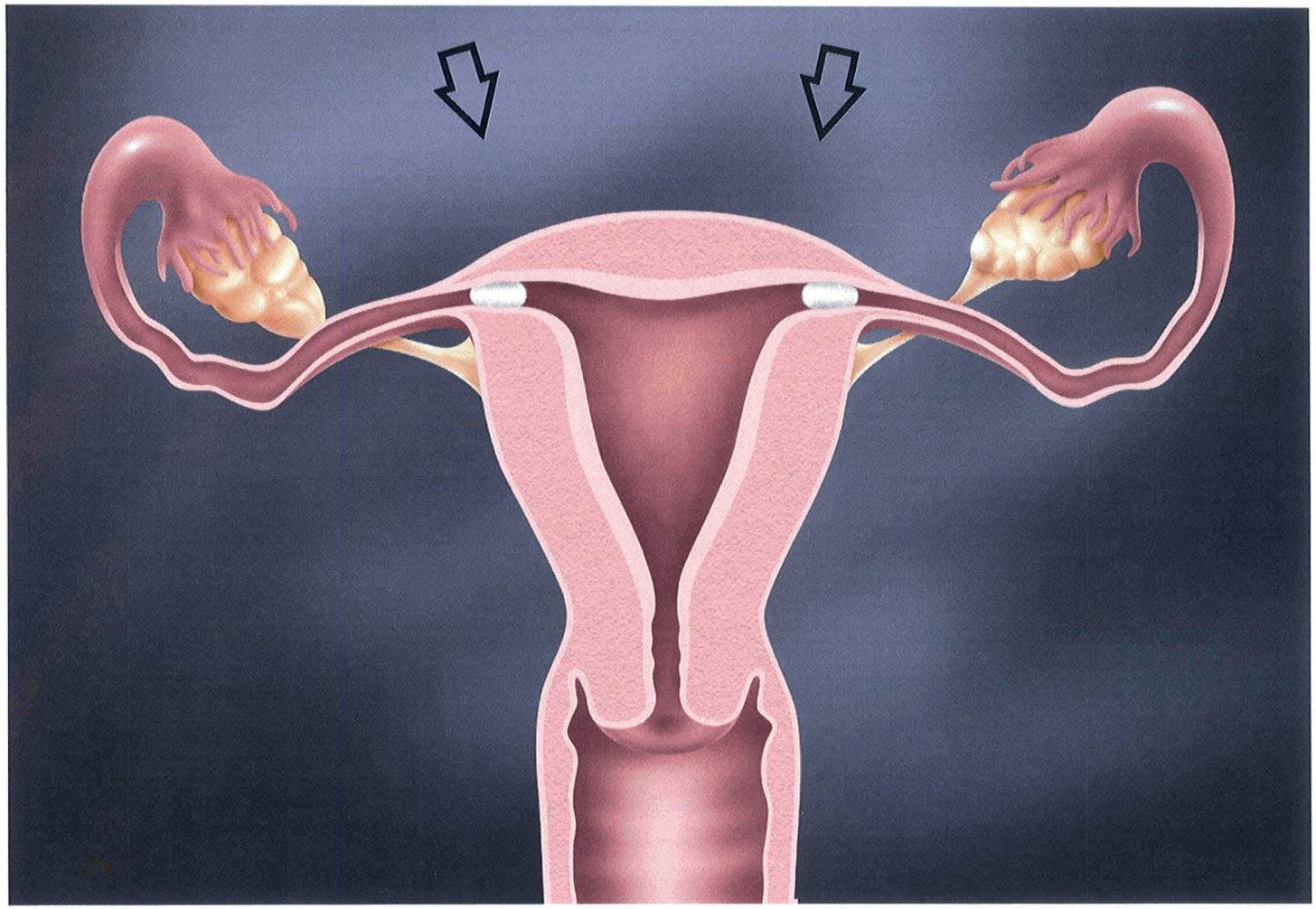
Performing the Procedure

- Mechanism of Action
- Equipment
- Background

Adiana Method

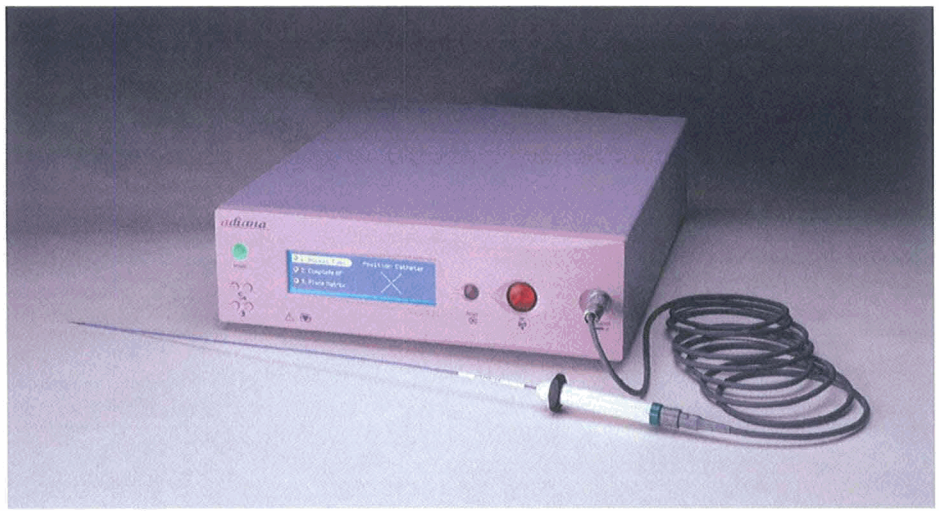
- Two step transcervical approach to permanent contraception.
  - Controlled thermal lesion within the intramural portion of the fallopian tube.
  - Placement of a porous biomaterial implant resulting in tissue ingrowth and tubal occlusion.

Adiana Matrix Placement

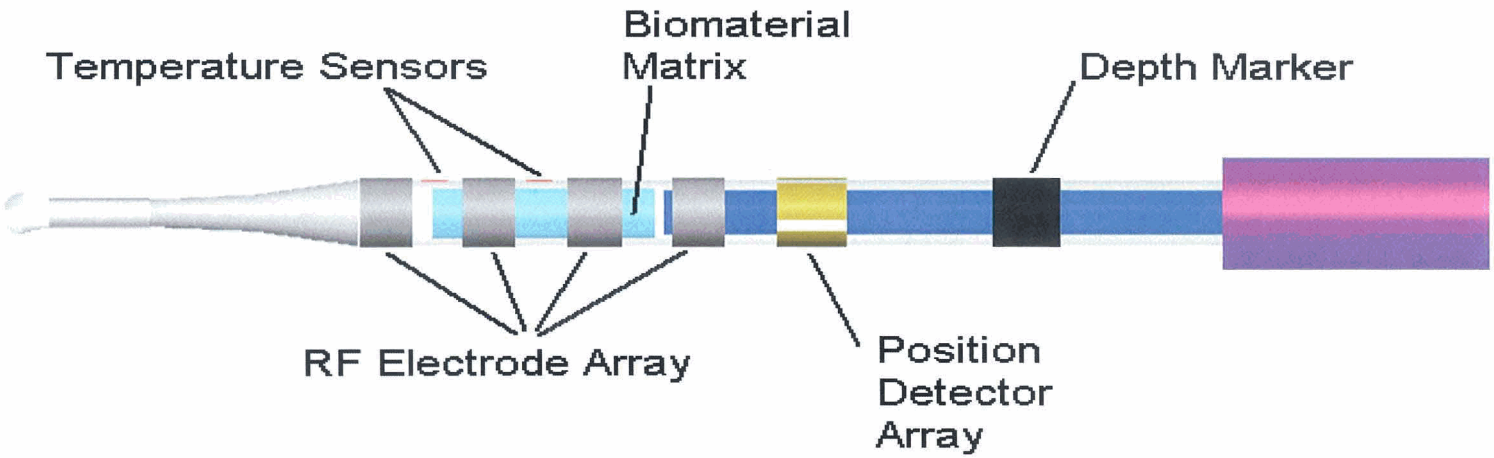


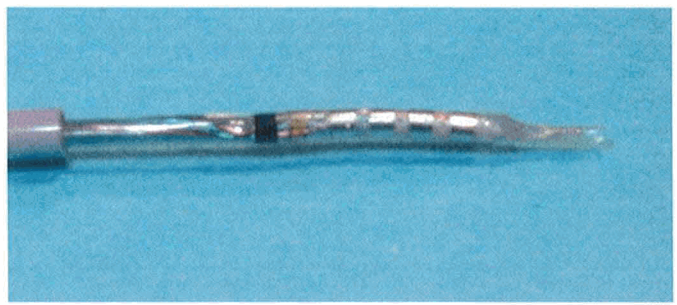
Device Overview

- Adiana Delivery Catheter
- Adiana Matrix
- Adiana Radio Frequency generator

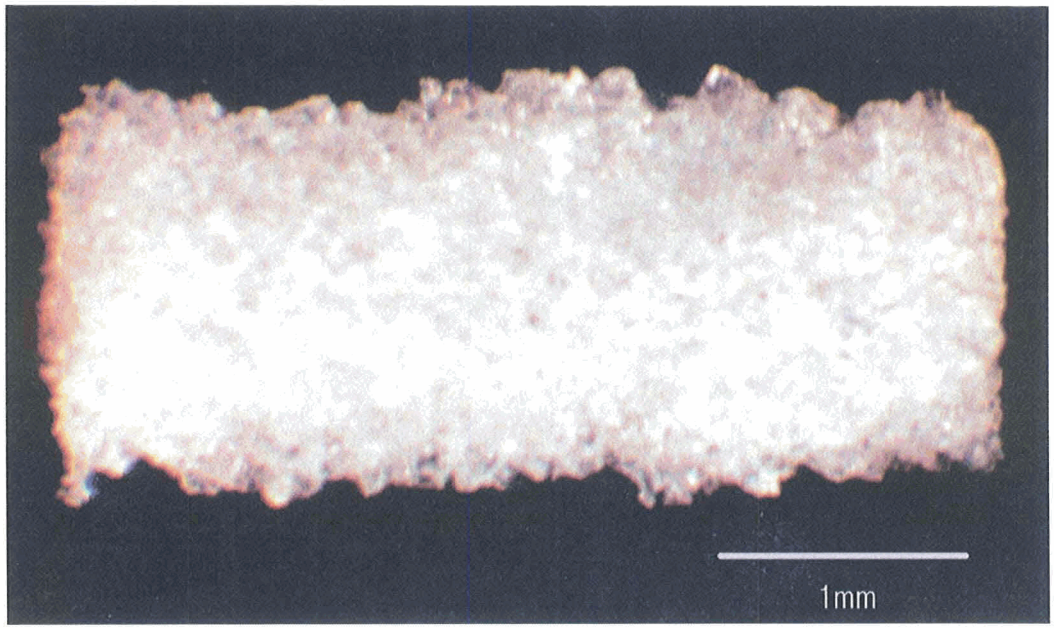


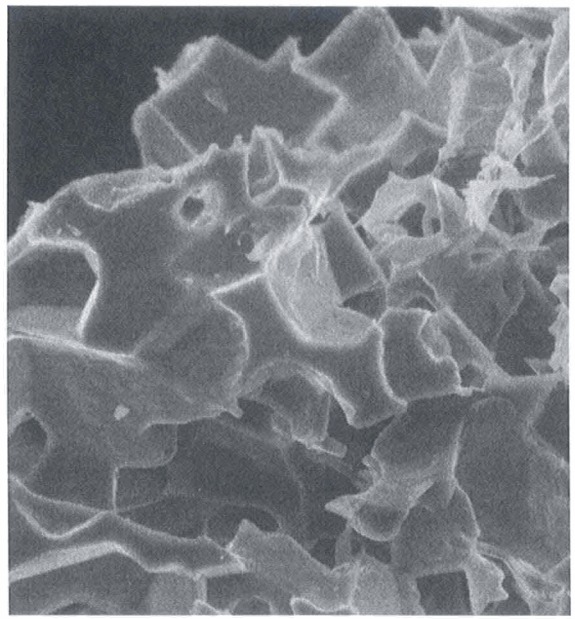
Adiana Delivery Catheter





Implantable Matrix





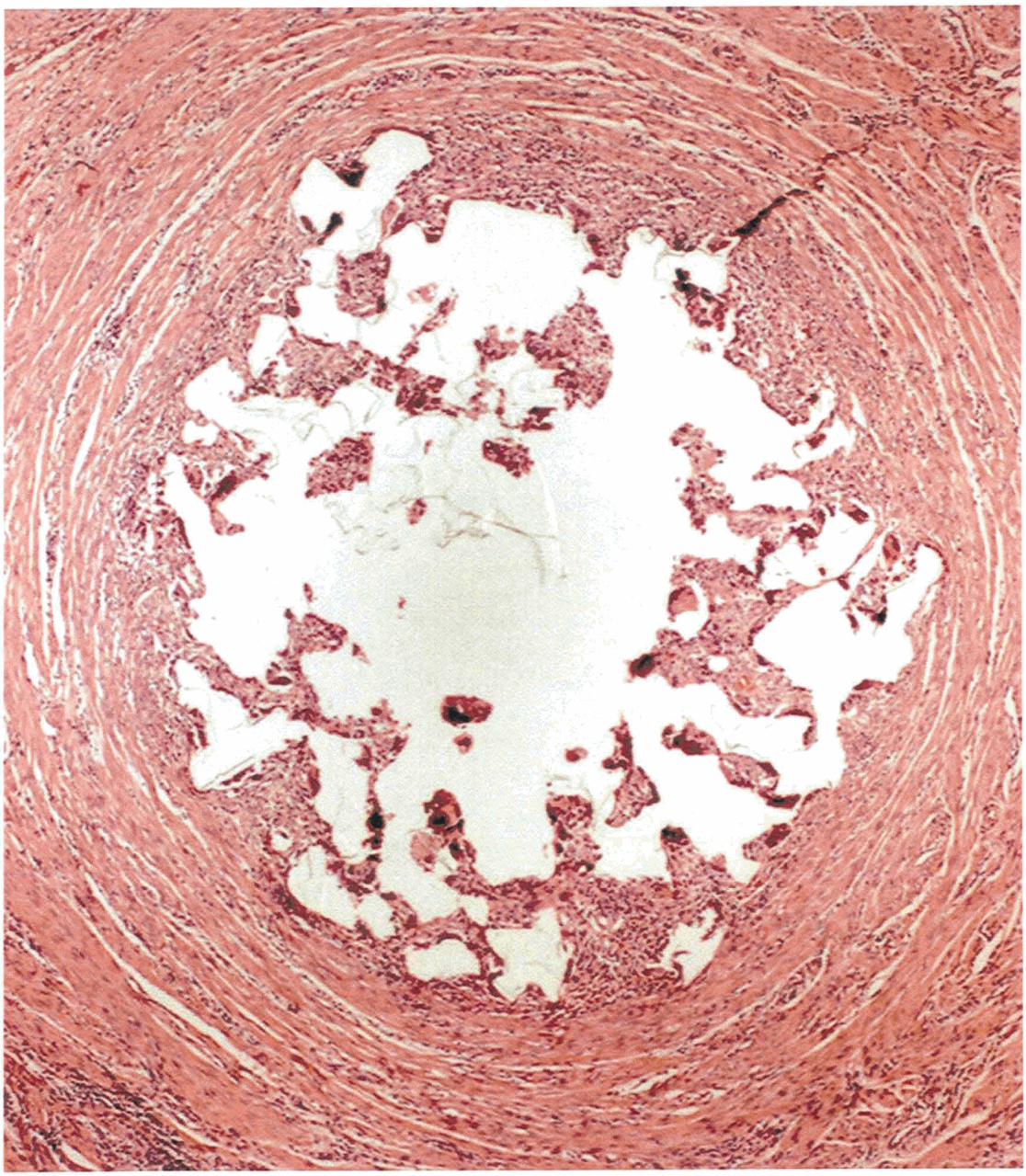
Porous Silicone

Adiana RF Generator

- Simplified User Interface
- Menu driven usage
  - Access Tube
  - Complete RF
  - Place Matrix
- No User selections for treatment parameters
  - Temperature (64°C) automatically controlled.
  - Duration (60 sec.) automatically controlled.

Mechanism of Action

- RF thermal lesion stimulates vascularized ingrowth.
- Matrix scaffold becomes integrated into tubal wall
- Ingrowth is space filling, vascularized and occlusive.

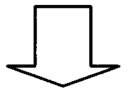


Insert procedure animation

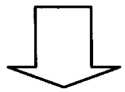
Prior Studies

In Vitro Studies

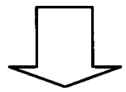
Animal Fertility Studies



Peri-Hysterectomy Studies



Access Studies



Pre-Hysterectomy Studies

EASE Clinical Trial

- Clinical Results as presented in SS&E

Adiana Procedure

- Equipment
- Patient Preparation
- Prior to Procedure
- RF Generator
- Hysteroscopic Access
- Tubal Access and Treatment
- Delivery Catheter and Matrix Placement
- Post Treatment

Room Set-up

- Large enough
- Adjustable table and comfortable stirrups
- Adiana RF Generator
    - Needs to be easily viewed and within cable reach of hysteroscope
- Hardware tower for hysteroscopy
- Mayo stand for instrument set-up
- Vital monitoring equipment per local requirements

Anesthesia Requirements

- Decisions regarding anesthesia reside with treating physician and patient
- Analgesia / anethesia needs to be adequate to keep the patient comfortable during procedure

Hysteroscopy Hardware

- Monitor
- Camera
- Light source and lead
- Fluid monitor

Hysteroscopy Operative Scope

- Continuous flow
- Rigid thin lens system
  - 2 to 3 mm diameter
  - Forward oblique view
  - 5F working channel

(Minimum)

Hysteroscopy Ancillary Supplies

- Tenaculum
- Hegar 4-5-6 or 'os finder'
- Open-sided speculum
  (removable once hysteroscope
  is in the cervical canal)

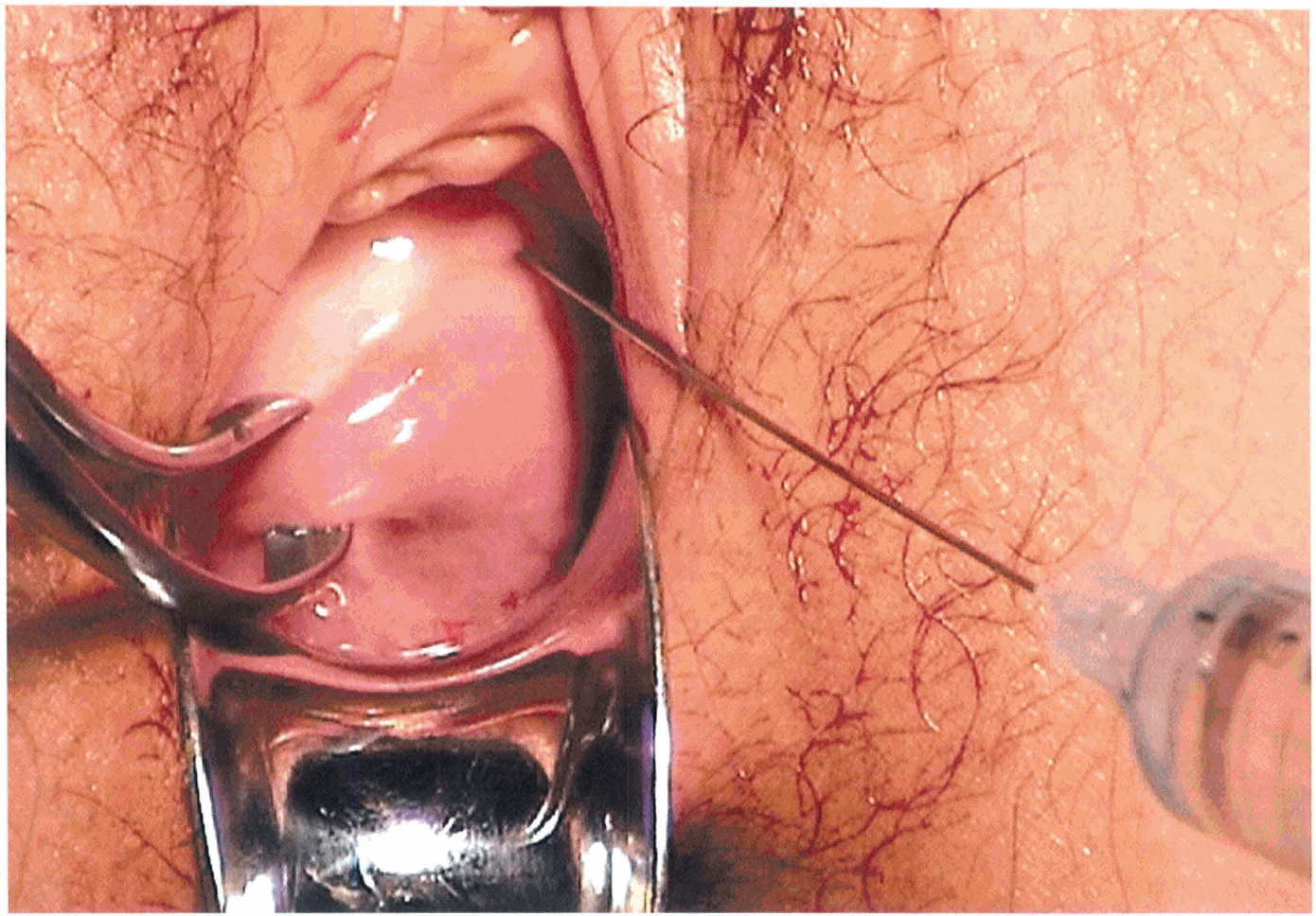
Hysteroscopy: Potential for Fluid Overload

- Any system with high pressure inflow increases the risk for fluid overload.
- The duration of the procedure and total volume of fluid applied should be monitored to ensure that fluid overload does not occur.
- Inflow and outflow should be monitored by medical staff.
- To reduce the risk of hyponatremia, the procedure must be immediately terminated if the fluid deficit exceeds 800cc.
- Additionally, the procedure time should not exceed 30 minutes.

Hysteroscope Placement - step 1

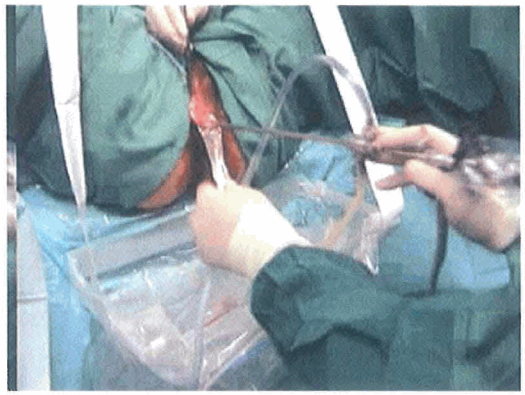
- Disinfection
- Place speculum
- Local anesthetic to cervix as per physician discretion

Application of Local Anesthetic to Cervix



Hysteroscope Placement - Step 2

- Connect hysteroscope to inflow, outflow and light cord
- White balance the camera
- Place the hysteroscope into the external os of the cervix and advance into the canal
- Remove the speculum



Hysteroscopic Orientation

- Use light cord attachment as the point of reference
- Keep camera in the vertical position at all times

Hysteroscope Placement – Step 3

- Keep the image of the cervical canal central in the lower third of view
- Pass internal ostium slowly (this is most common trigger for vagal reaction)
- Place hysteroscope in neutral position
- Visualize ostia by rotation to the left and the right

Identification of Tubal Ostia

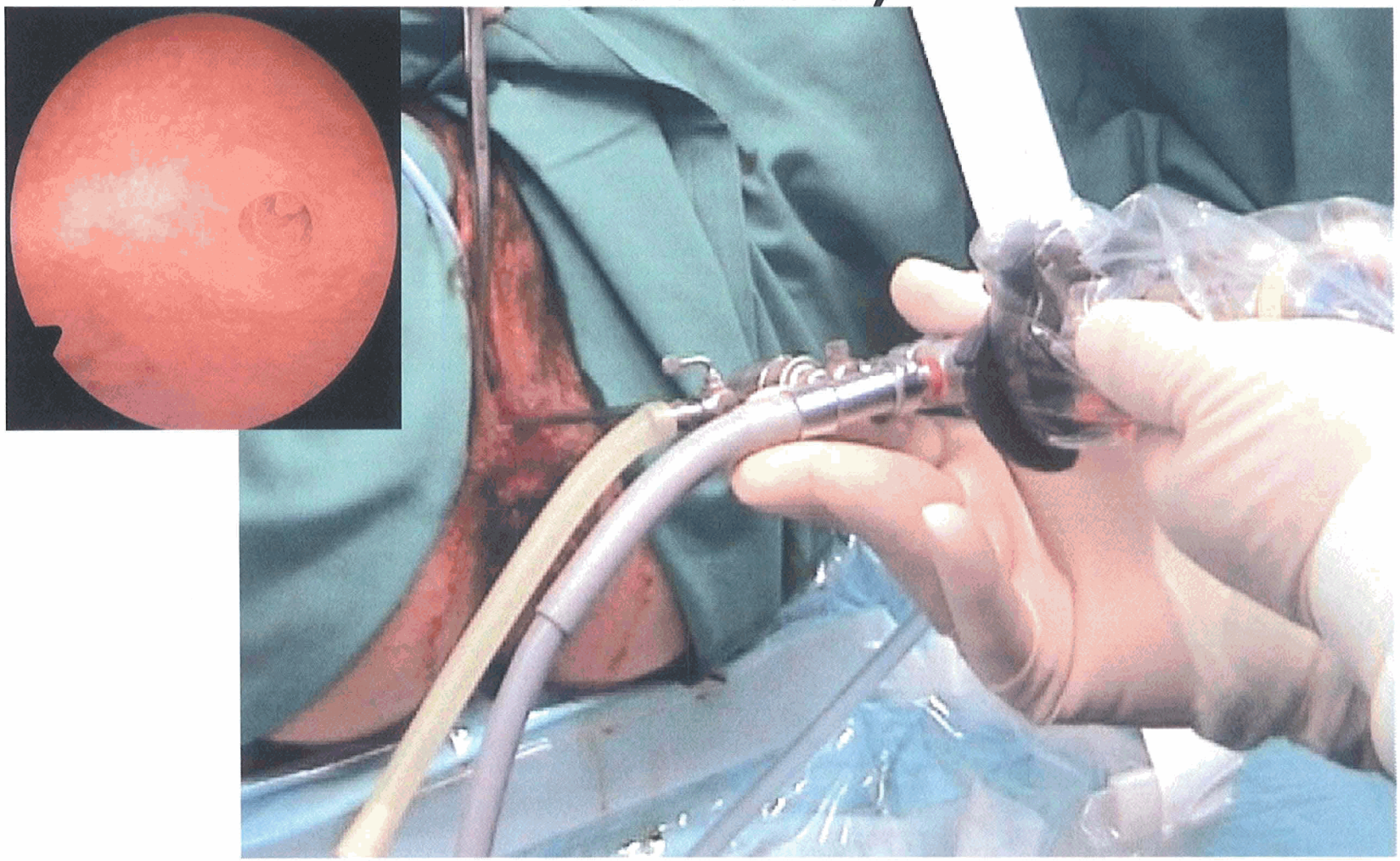
- Three cardinal positions of the hysteroscope:
  - Neutral
  - Left Access
  - Right Access

(video Clip provided here)

Catheter placement (neutral position)

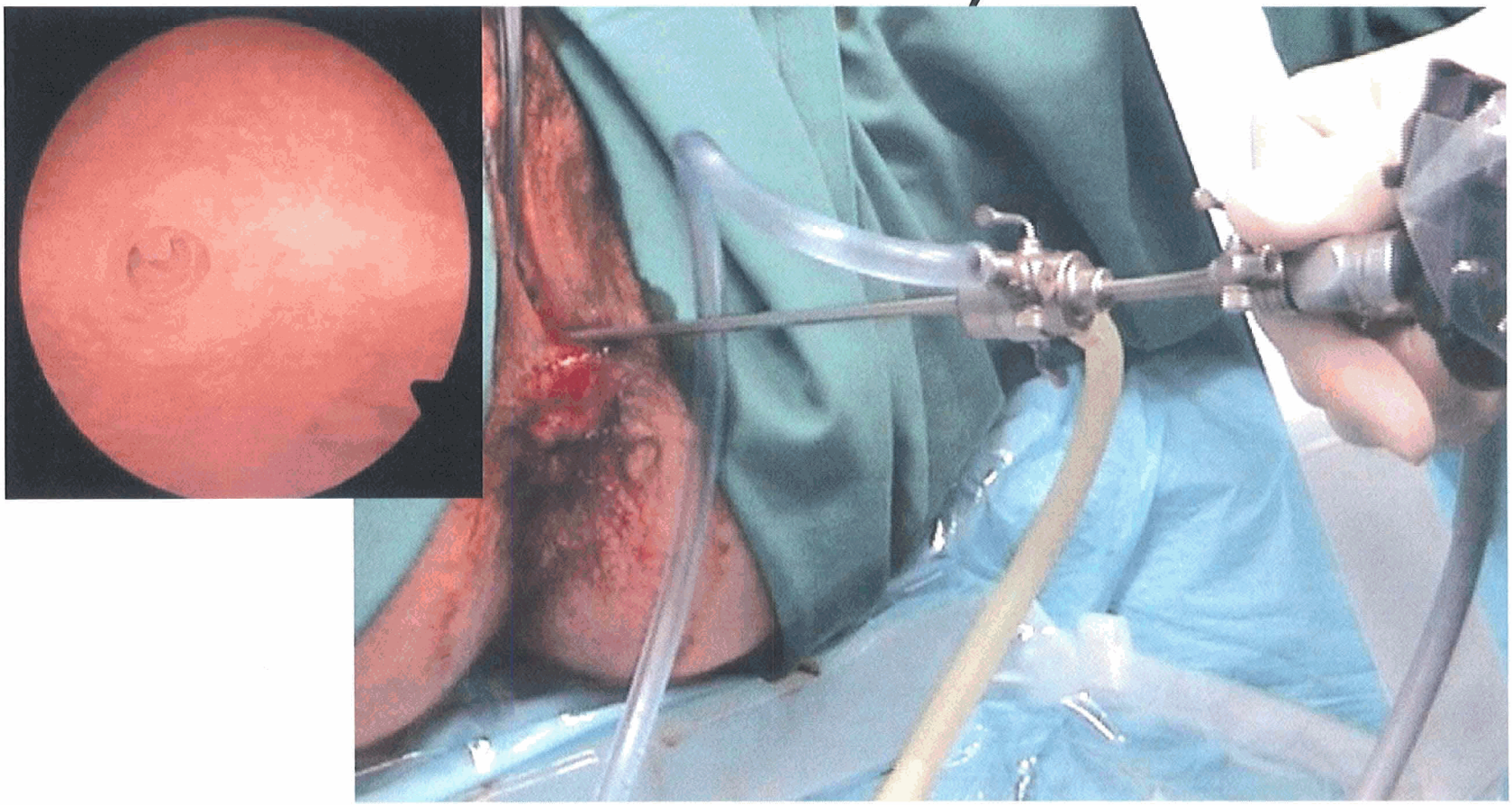
Video clip provided here

Catheter placement (left access)



Video clip provided here

Catheter placement (right access)



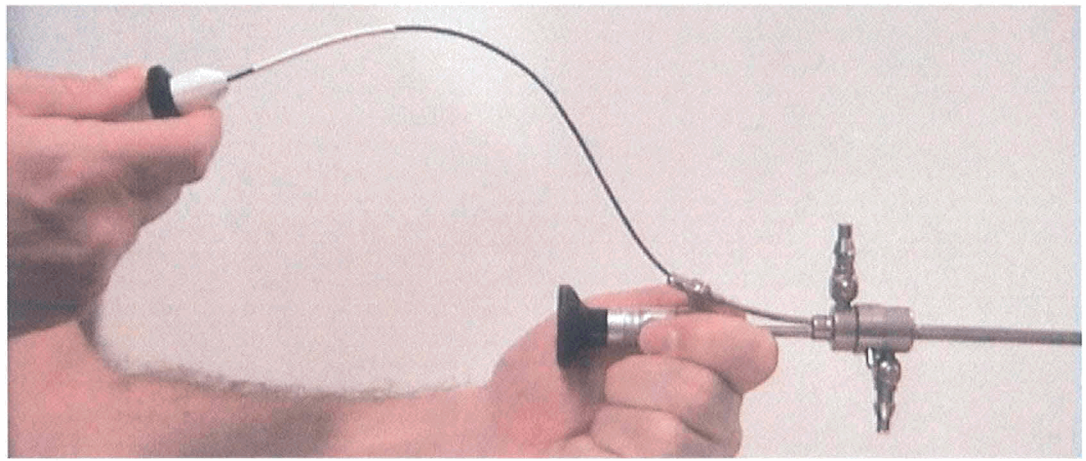
Video clip provided here

Catheter Placement – Step 4

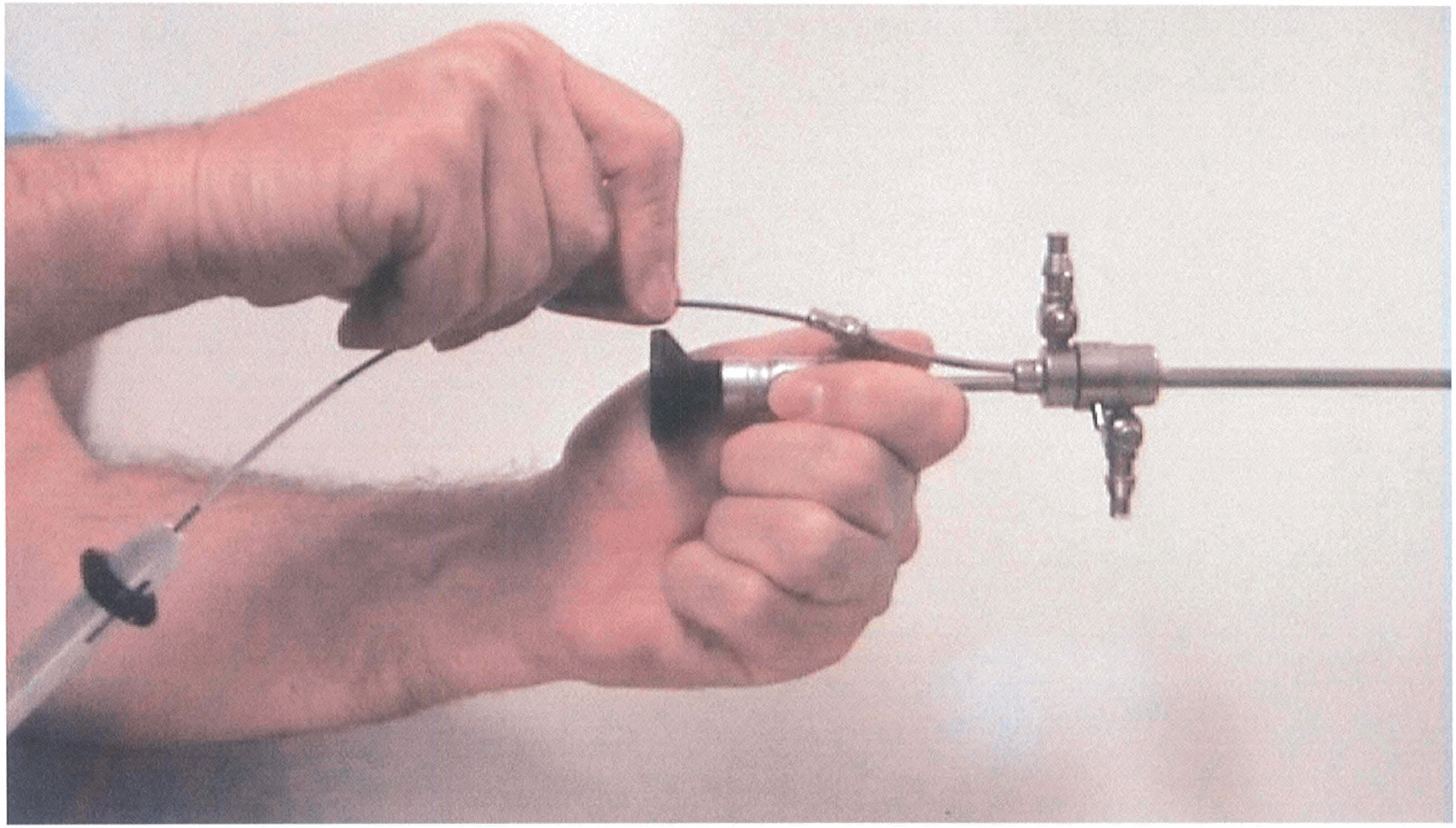
- Connect Delivery Catheter to cable
- Open the valve of the working channel
- Place Split Introducer with mandrel into the grommet on the working channel – remove mandrel
- Place catheter into Introducer
- Feed the catheter into the channel
- Remove Introducer
- Advance catheter until tip is in hysteroscopic view

Catheter Handling

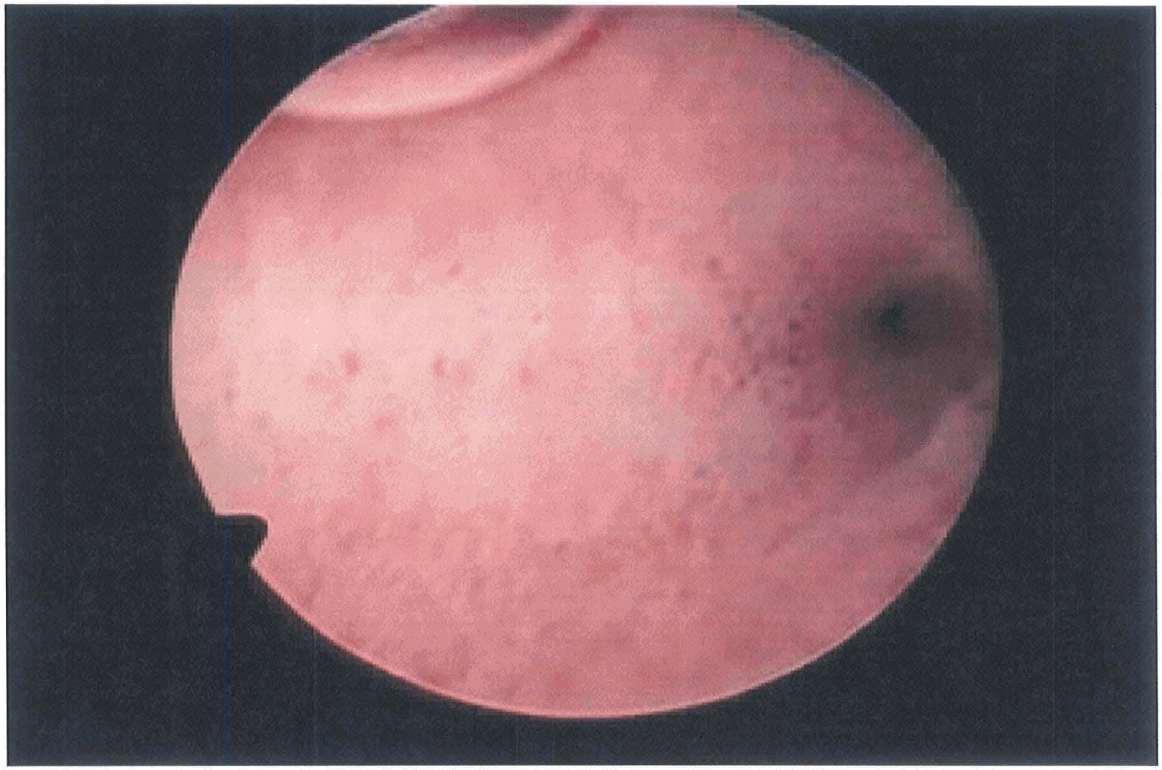
- Avoid damage to catheter tip when inserting into working channel
- To advance the catheter with greatest ease, the length of unsupported catheter should be kept to a minimum at either end of the scope.



Catheter Handling

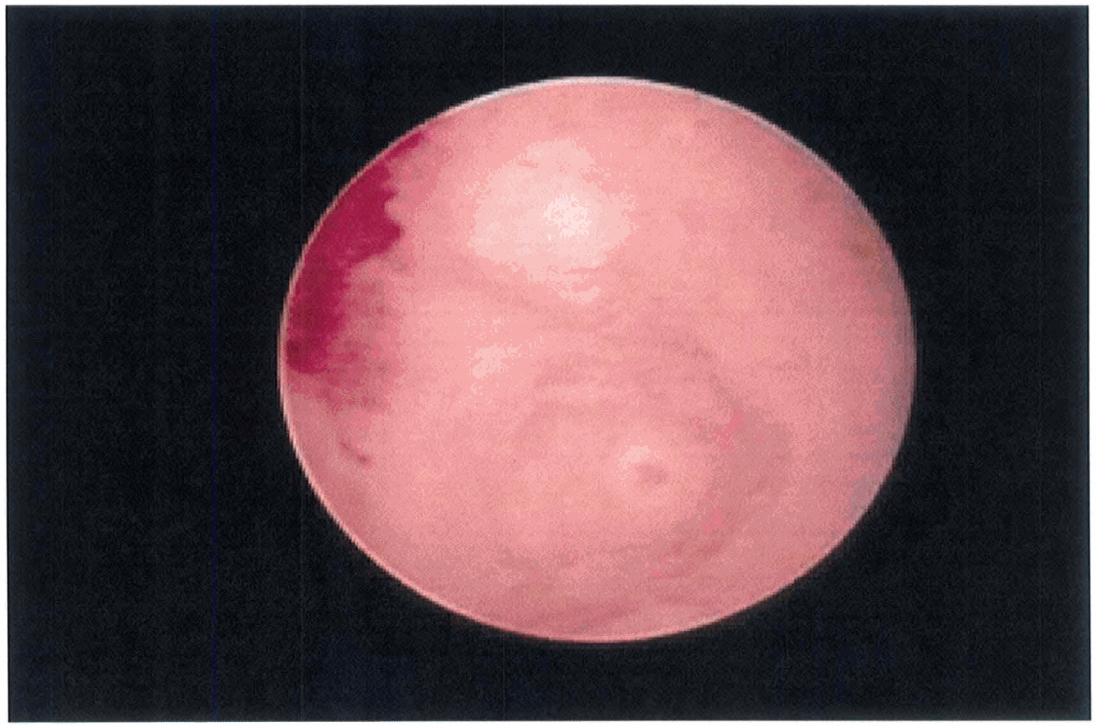


Ostium Identification



Video clip provided here

Access Failure



("Cannot Reach Black Mark" video)

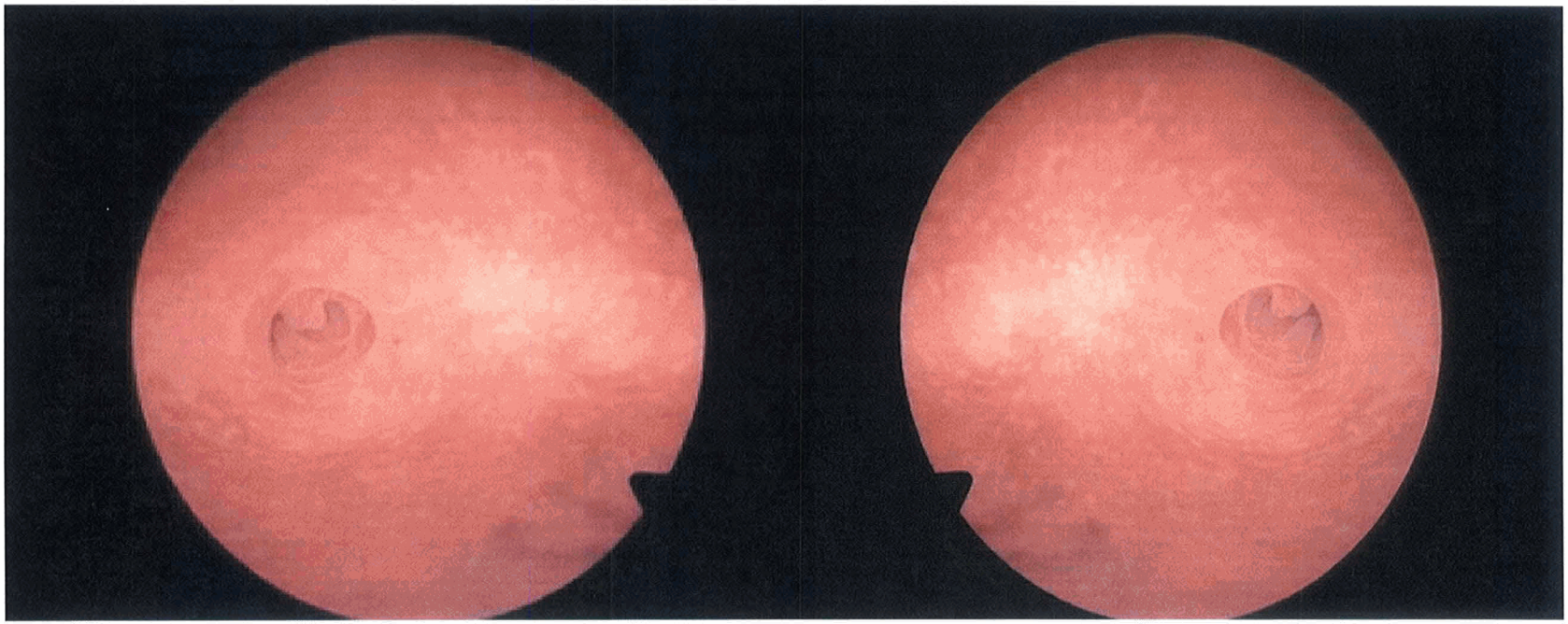
Catheter Placement – Step 5

- Rotate hysteroscope into left access position
- Bring tip of catheter toward the ostium
- Adjust alignment of catheter mainly by rotation

Catheter Placement – Step 6

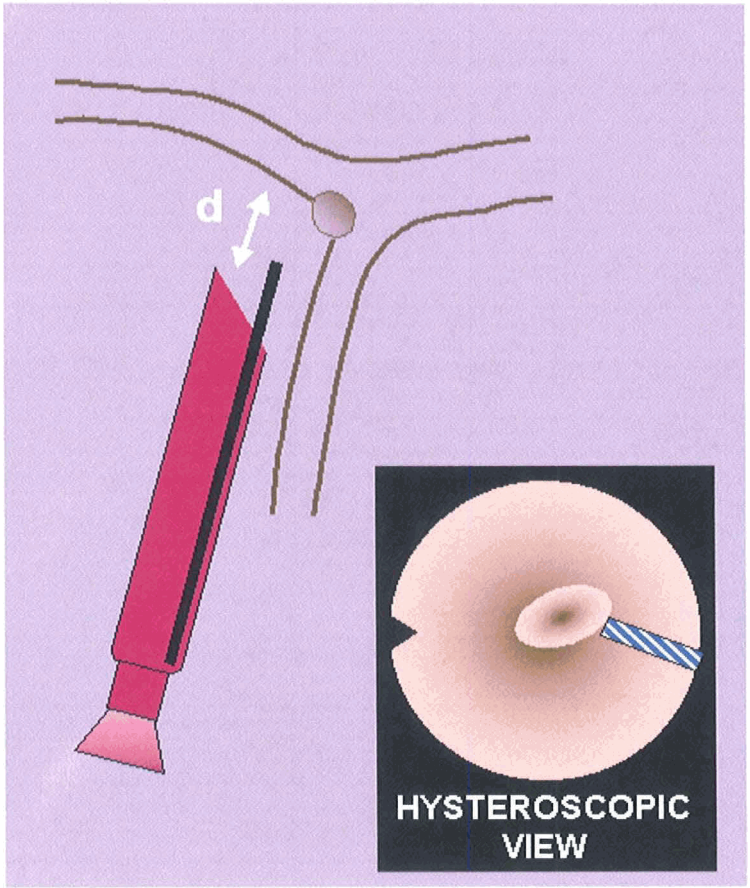
- Advance catheter and scope to shorten the unsupported length of the catheter
- Advance the catheter up to the black mark once the scope reaches the uterine wall

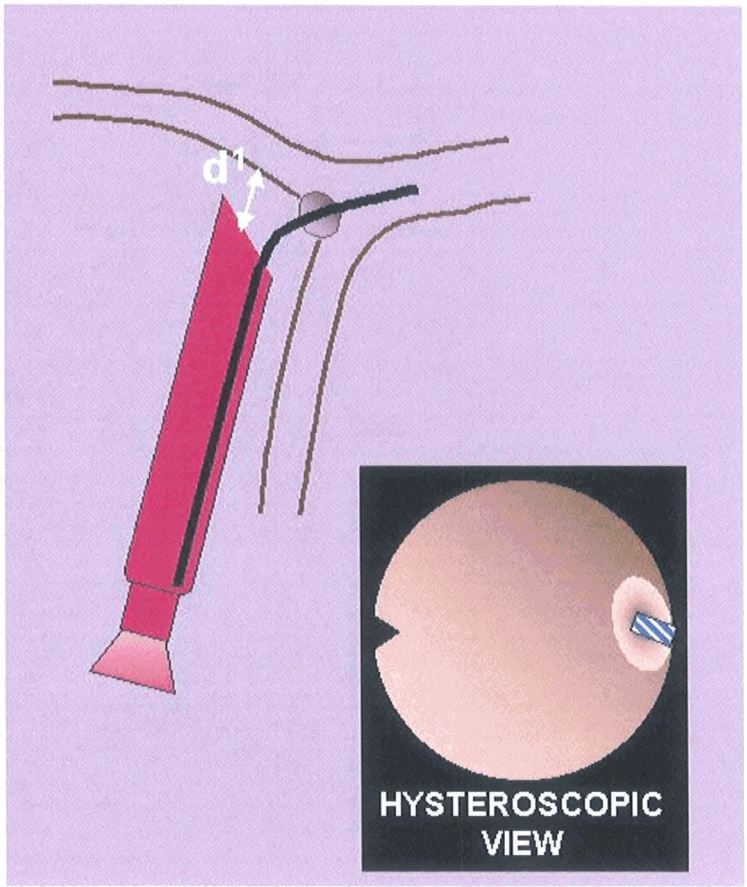
Catheter placement



Video of cannulation and advancing to the black mark

Hysteroscopic Orientation for Catheter Advancement





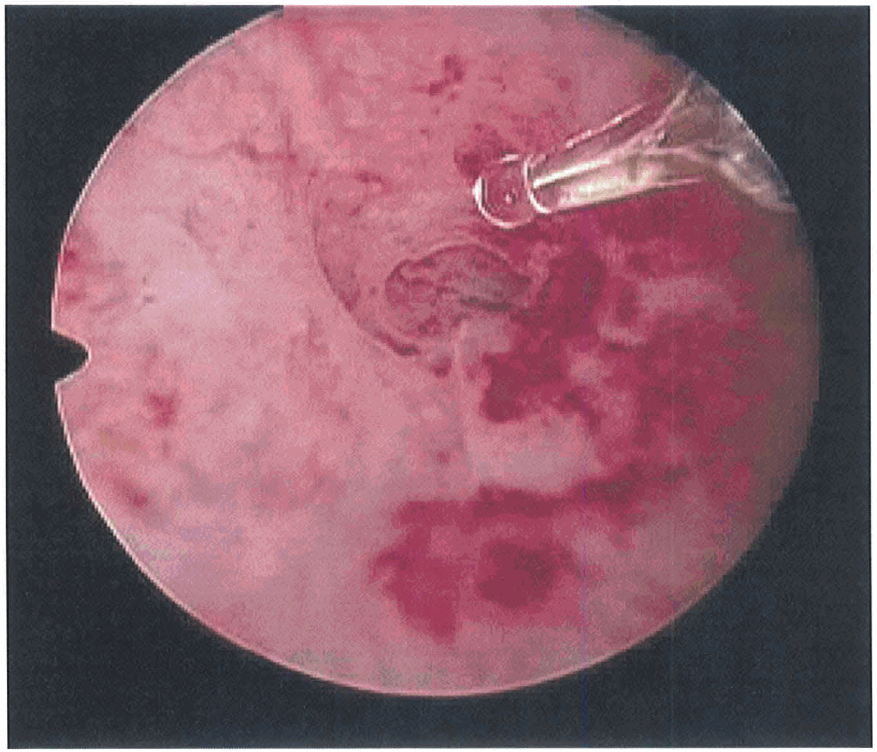
Catheter Placement – Step 7

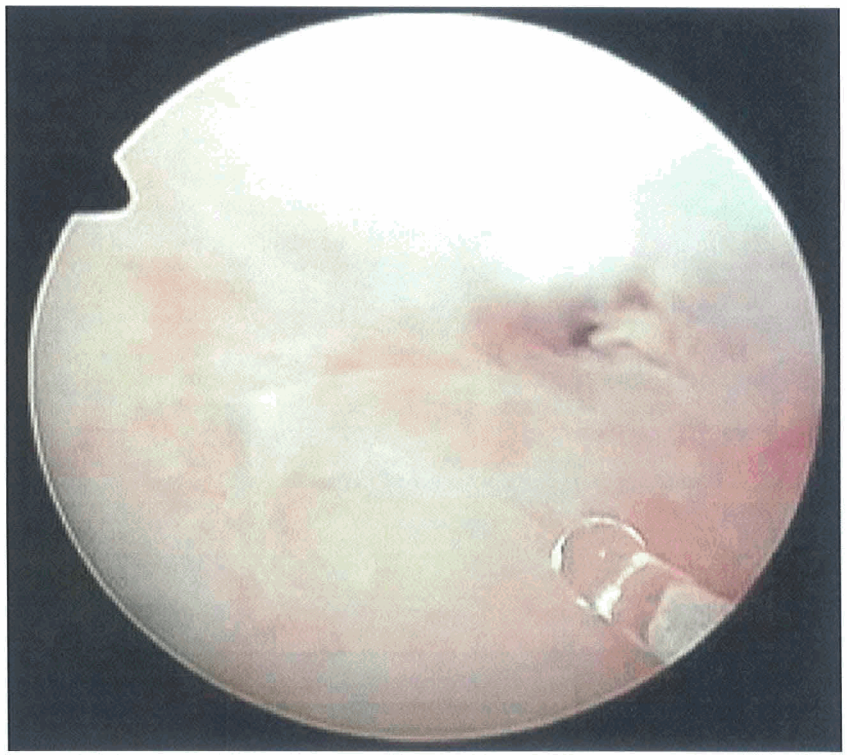
- Keep catheter in place and slightly withdraw the scope to increase panoramic image
- Position scope such that the ostium and the shaft are in view

Why Is Visualization of Shaft Important?

- At end of RF, black mark will be moving backwards as matrix releases- cannot make sure device is steady unless shaft is observed continually
- Following RF treatment, the black mark will be moving as the Matrix releases
- Visualization of shaft and ostium will ensure that a steady position is maintained

Good view of catheter in place





Video clip inserted here

Proper Placement Technique

- View – distal view can distort appearance
- Approach os with scope and confirm
- Check PDA
  - Intermittent PDA contact may lead to failure to achieve 60 second RF treatment- stable signal more likely to lead to RF success

Adiana RF Procedure – Step 8

- Optimize PDA
  - All 4 quadrants
  - Steady PDA signal
  - Advance to ‘true os’ if necessary
- Ensure Visualization of:
  - Black Mark
  - Ostium
  - Catheter Shaft
- No Movement once in position
- Start RF
- System tones audibly at end of 60 sec RF

Matrix Placement – Step 9

- Activate Matrix Release-
  - Do not advance or withdraw catheter
  - Simple press Matrix Release Button on the handle
- Remove Catheter from ostium after RF Generator signals Matrix release

End of Release

- RF Generator will beep
- Look for blue push rod
- Remove catheter
- Repeat procedure for contralateral side

Patient Discharge

- Advise on need for alternative contraception until HSG results are known
- Send patient home with general instructions

Confirmatory Visit

- Three months
  - Perform HSG
  - End alternative contraception if tubes occluded
- Special instructions on performing HSG for tubal occlusion evaluation can be found in the Adiana HSG Procedure Manual

Managing Challenging Cases

Procedural Challenges

- Visualizing the Ostia
- Tubal access
- PDA Contact
- RF Treatment
- Matrix release
- Technique
- Re-treatments

Visualizing the Ostia

- Polyp or myoma
- Excessive endometrium
- Blood or debris in the uterus
- Poor uterine distension
- Folds of uterine tissue
- Poor lighting from the fibro-optic

Tubal Access

- When, despite good alignment, increased resistance prevents the catheter from smoothly advancing into the tubal lumen, refrain from excessive force and consider the following factors:
  - An improperly oriented catheter can interfere with tracking within the tubal lumen: orient hysteroscope to align the catheter axis with the apparent tube axis.
  - The hysteroscope may not be positioned closely enough to the ostium. Although close proximity of the optic to the object reduces visualization, the operator will be better able to avoid kinking of the catheter.

Tubal Access

- When the hysteroscope working channel is too large, the catheter does not receive enough proximal support: Use a smaller working channel hysteroscope
- When the hysteroscope is too far back, the catheter does not receive enough proximal support. In this case, the hysteroscope should be moved forward for best results.
- During the procedure, the catheter can become kinked or damaged. When this occurs, replace the catheter.

Tubal Access

- If the catheter is inserted into a false ostium or tube, remove the catheter and repeat the catheter placement. Visually confirm that it has been placed in the true ostium.

- To reduce the risk of perforation, advance the catheter until the most proximal edge of the Black Mark is at the ostium but no further. Typically slight resistance is felt at this point.

- Do NOT advance the catheter past the intramural portion of the fallopian tube. While this point cannot be identified during the procedure, knowledge of the patient's uterine wall thickness, and the fact that the length of the Adiana catheter from black marker band to distal tip is 14 mm can be used as a guide to allow the operator to safely advance.

Position Detector Array (PDA) contact

- If the PDA does not indicate adequate circumferential contact, yet the Black Mark appears to be at the tubal ostium, the following should be considered:
  - If the catheter is angulated, or forced up against one side of the ostium, the PDA may not be in good contact. In this case, relieve pressure to see if contact is improved.
  - If the device is not up to black mark, advance the device into the tube up to the black mark.
- Occasionally the Delivery Catheter tip is inserted into a 'false' ostium. To investigate this possibility, retract the Delivery Catheter and locate the true ostium by advancing the hysteroscope up to the ostium and looking past the first ring of tissue (the so called "false" ostium). Insert the Delivery Catheter into the true ostium up to the Black Mark.

RF Treatment

- RF Energy delivery may be interrupted due to:
  - Excessive movement
  - Loss of PDA contact
  - Electrical or thermal errors detected by the RF Generator
  - Inadvertent catheter removal prior to matrix release

- In this case the following should be done:
  - Identify the fault code from the generator front panel
  - Refer to the RF Generator manual for specific instructions
  - Correct the source of the fault (as described)
  - Perform a generator reset (if indicated)
  - Determine how many seconds of RF energy have been delivered
    - If less than 60 seconds, a repeat treatment is permitted provided that the maximum total RF energy delivery period for any single tube does not exceed a TOTAL of 120 seconds
  - The operator should reposition or replace the Delivery Catheter and repeat the RF delivery and subsequent Matrix placement.

General RF Generator Faults

- The RF Generator Specification and Installation Guide contains information about *recoverable* and *non-recoverable* errors.
  - For a *recoverable* error, press Reset and continue with procedure
  - For a FAULT (*non-recoverable*), it is necessary to power off, then power on the RF Generator. If the problem persists, it will be necessary to contact Cytyc service.

Repeat Treatment

Treatment may be restarted providing that:

- TOTAL treatment time does not exceed up to 120 seconds
- Complete treatment (60 seconds immediately followed by Matrix release) can be attained

Matrix Ejection

- In the rare event of a Matrix Ejection Failure, repeat the procedure with a new catheter.
- If accidental Matrix placement occurs during the RF Cycle, check to see whether the matrix has fallen out of the tube or might still be within the tube. If it can be seen, remove it and repeat the procedure.
- Unless the patient has received 60 seconds of RF followed by matrix placement, the patient should not rely on the Adiana Procedure and should be offered alternative treatement.

Technique

- Maintain sufficient distention pressure throughout the procedure
- Minimize the force required to position the sheath mark up to the ostium – steady gentle pressure better than forceful motions
- Assess the “true” tubal ostium
- Before starting the RF cycle:
  - Position the hysteroscope in a comfortable position
  - Position hand comfortably on the device handle and release button

Technique

- Control patient movement and comfort
- If significant movement occurs and/or visibility is lost, it is recommended that the procedure be temporarily stopped and restarted once movement is controlled and/or visibility regained
- After Matrix release, do not remove the catheter until the generator audibly signals to do so

VIII. B. 2. HSG TRAINING

Cytyc Surgical Products

Adiana Transcervical Sterilization System

Adiana HSG Protocol
Physician Training

Performing the Three Month Follow up HSG

Normal Practices

- Instructions provided herein are not intended to replace normal practices at your institution, but are provided as a guiance.
- Minimum standards for performing Hysterosalpingogram (HSG) are contained in the instruction document:

  Adiana HSG Protocol
- A copy of these instructions is provided with the training package and can be obtained upon request from Cytyc

CYTYC

HSG – Overview

- The HSG is to be performed by 3 months post device placement
- To prevent trauma to the tissue ingrowth and prevent rupturing the tubal blockage, uterine distention pressure should not exceed 200 mmHG (Bonchek Vein Distention System or similar)
- Keeping a cervical seal throughout procedure to maintain internal uterine pressure is essential
- Use Fluoroscopic equipment must be used to visualize radiopaque contrast filling.
- **Document final results with spot films**

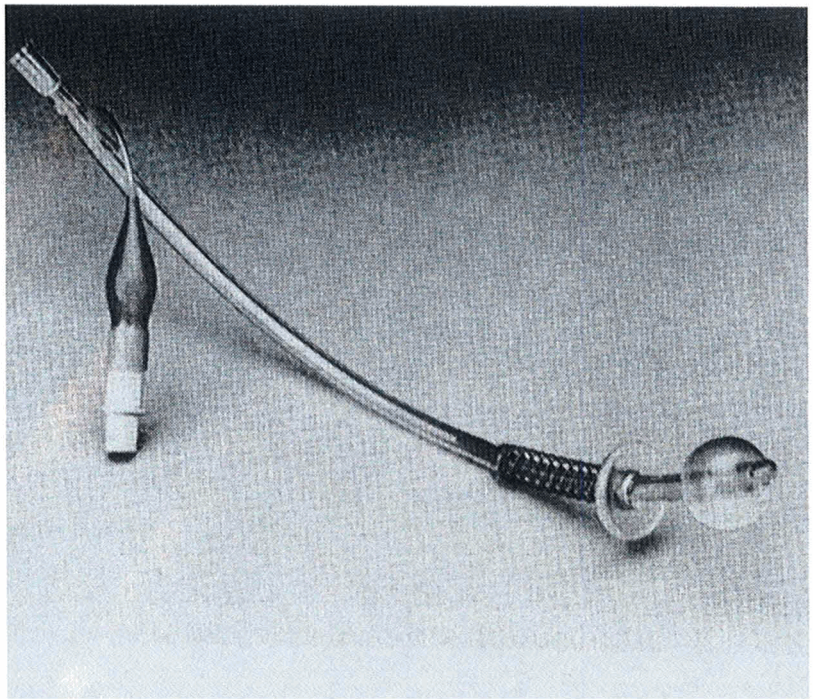
CYTYC

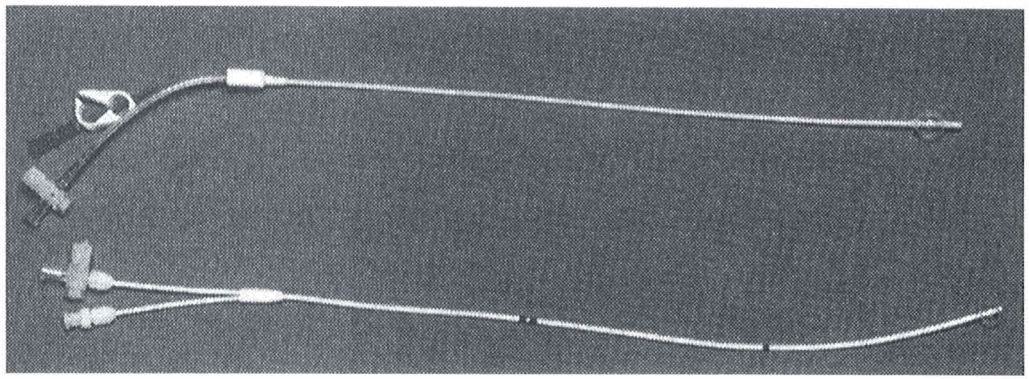
HSG Equipment

- Equipment for visualizing and cleansing cervix
- Catheter with Occlusion balloon cuff (or other suitable cannula based on local preference)
- Hypaque® Contrast (or equivalent water-soluble radiopaque contrast)
- 20cc syringe for Contrast Media
- Syringe for inflation of balloon cuff
- Sterile Saline for balloon inflation
- Pressure limiting device (Bonchek Vein Distention System 200 mmHg or similar)
- Tenaculum

CYTYC

HSG-Catheters





CYTYC

HSG Technique

- **Patient Placement -** The patient is placed supine at the end of the fluoroscopic table in a modified lithotomy position.
- **Sterile Field-** The cervical canal or endometrial cavity should be accessed using aseptic technique.
- **View and Clean Cervix -** A sterile double bladed metal speculum is inserted into the vagina to provide a clear view of the cervix. The cervix is cleaned with a disinfectant and the excess is wiped with a dry swab or sponge to prevent its passage into the uterine cavity. It is important to remove the metal speculum during Xray exposure to prevent the image of the speculum from overlying potential contrast media spill or cervical leakage.
- **Sealing Cervix and Injecting Contrast Medium -** Care should be taken to minimize cervical dilation so that a good cervical seal is easy to achieve and maintain throughout the HSG.
- **Remove Speculum** after catheter is in place. During Xray exposure, the image of the speculum may overlay potential contrast media spill or cervical leakage.
- Local Anesthesia is usually not required but may be necessary in some cases

CYTYC

Optimize Fluoroscopic View

- Six radiographs are recommended in order to unequivocally demonstrate tubal occlusion. For this procedure, the entire uterine cavity is gradually filled with enough contrast medium to challenge both cornu and to achieve full extension with clear visibility. The uterine cavity silhouette should be apparent and no critical structures should overlay confounding objects.

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Required Views

- **Images**
  - For the first four pictures the fluoroscopy beam should approximate A/P projection. If needed, reposition the image camera and inject additional contrast only if necessary. A suggested sequence is described below.
- **(1) Scout radiograph**
- **(2) Partial Fill**
- **(3) Cervical seal/ Complete Fill**
- **(4) Cornual visualization**
- **(5) Right Lateral Oblique**
- **(6) Left Lateral Oblique**

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Image 1: Scout radiograph

- The first picture should be taken to ensure a normal uterine cavity without adhesions and/or other pathologies.
- [Insert Image 1- Scout Radiograph]

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Image (2) Partial Fill

- A second picture should be taken as the contrast is injected to confirm proper position of the uterus and adequate anatomical visualization.

[Insert Image 2 – Partial fill of uterine cavity with contrast media]

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Image (3) Cervical seal/ Complete Fill

- A third picture should be taken as additional contrast medium is injected to confirm a good cervical seal and indicate complete filling of the uterine cavity.

[Insert Image 3- Fully distended uterine filling]

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Image (4) Cornual visualization

- A fourth picture should be take to demonstrate maximal distension of the cornual area and adequate filling of the uterine cavity. If necessary for full cornual visualization, a tenaculum can be used to apply tension to the cervix. However, too much tension on the cervix can trigger a vagal reaction.

[Insert Image 4- Fully filled cornua]

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Image (5) Right Lateral Oblique

- To better capture the right fallopian tube and create separation from underlying structures, ask patient to rotate slightly, placing right the knee on the left side of her body for a right lateral oblique radiograph.

[Insert Image 5 - right lateral oblique radiograph]

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Image (6) Left Lateral Oblique

- Repeat the Right Lateral Oblique procedure on the left side.

[Insert Image 6- Left lateral oblique radiograph]

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Required Views

- Once contrast media has filled the uterus, continuously optimize fluoroscopic views.
  - Ensure cornu are clearly visible and the entire cavity is filled with contrast.
  - Make sure critical structures are visible and no critical structures overlay confounding objects.
  - Reposition image camera if needed. Inject more contrast if required.
  - Rotate patient for Lateral oblique views
- Expose the single film frames as study progresses to capture required views as described.
  - Shoot sufficient films to demonstrate tubes are closed
  - Develop and check quality.
  - If acceptable, remove equipment from patient

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Evaluating HSGs

- When evaluating the HSG, it is important to first confirm that the appropriate radiographs described above are provided, a good A/P image of the uterine silhouette is obtained, and the uterus is maximally distended in at least one view. The HSG will need to be immediately repeated if:
  - The appropriate sequence of radiographs has been captured but one or both uterine cornua are not maximally distended;
  - The projection of the silhouette is fundal rather than A/P;
  - The appropriate sequence of radiographs was not taken, and/or the uterine cornua are not distended or are otherwise obscured making evaluation of the image impossible or equivocal.

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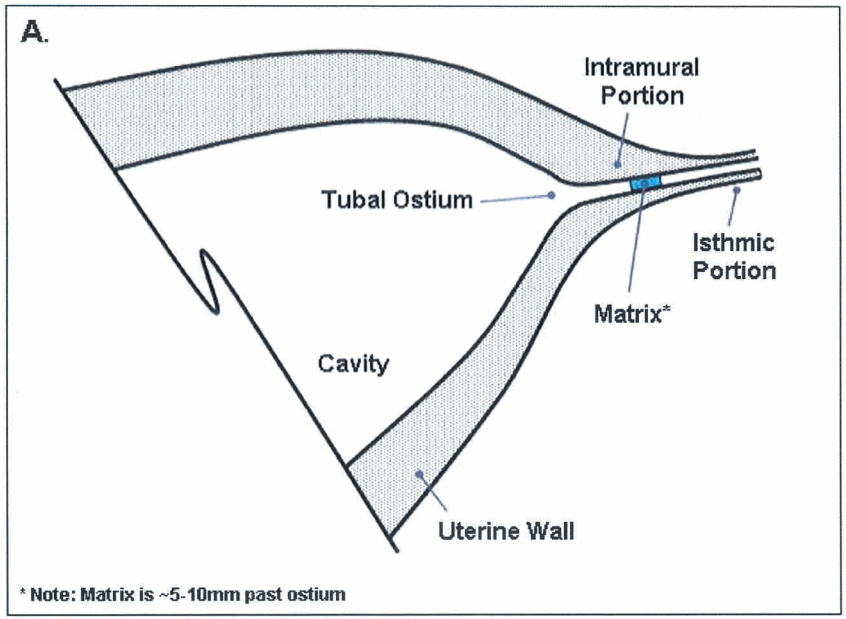
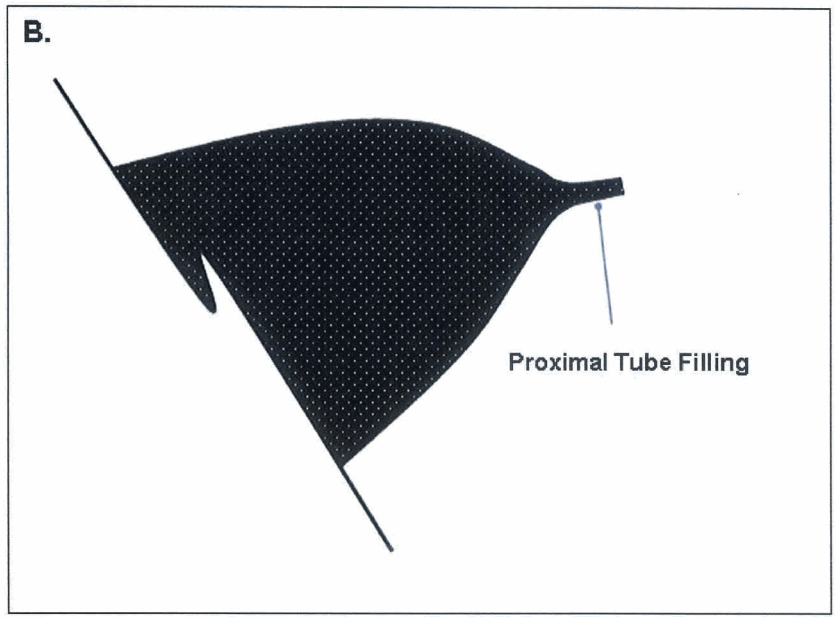
Adiana Matrix Location





The Adiana matrix is delivered into the intramural portion of the fallopian tube. The drawing depicts the matrix location (A), as well as the resulting HSG image (B):

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HSG - Criteria

- Tubal Occlusion
  - HSG blocked at matrix location
- Failure to Achieve Tubal Occlusion:
  - Differentiate from peritubal extravasation
  - HSG Contrast located distal to matrix location

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Patient Management

- Patients with patent or inconclusive HSGs should be advised to continue relying on alternate contraception for an additional three months. They should be advised NOT to rely on the Adiana implant for contraception at this time.
- The HSG protocol should be repeated in three months. If bilateral occlusion has not been achieved at that time, the patient should be counseled to seek an alternate means of contraception.

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Repeat Tests

- If results are equivocal or patent after three months of waiting, advise the patient to continue using alternative contraception. Repeat the HSG in three months. (If the HSG was non-diagnostic due to technical issues, an immediate repeat may be considered.)

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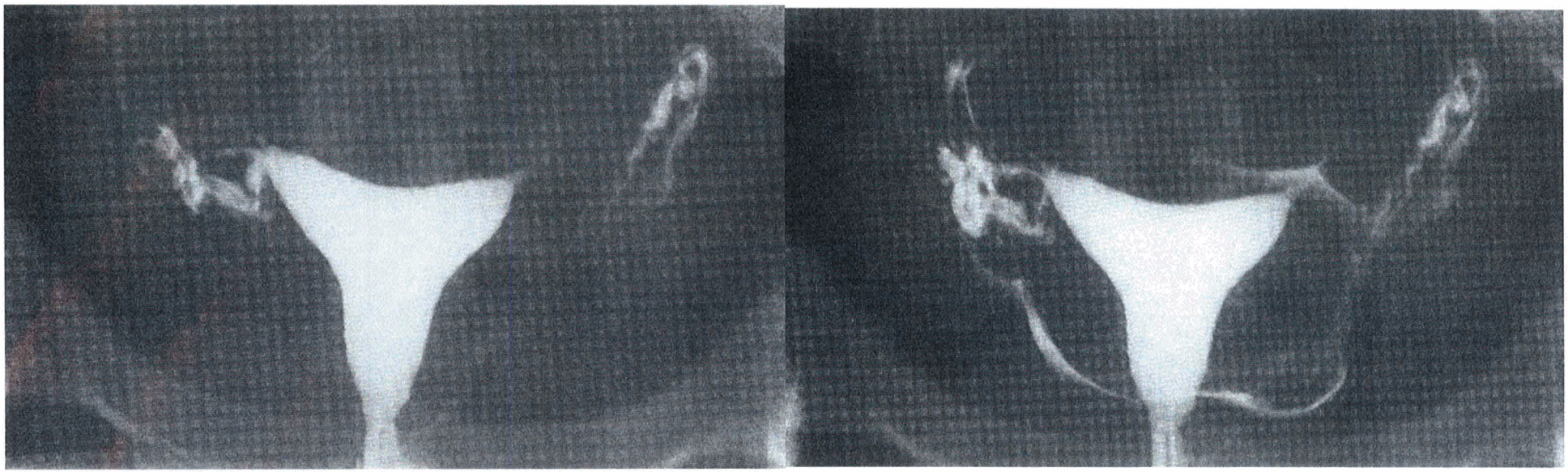
HSG-Normal Unblocked Tubes



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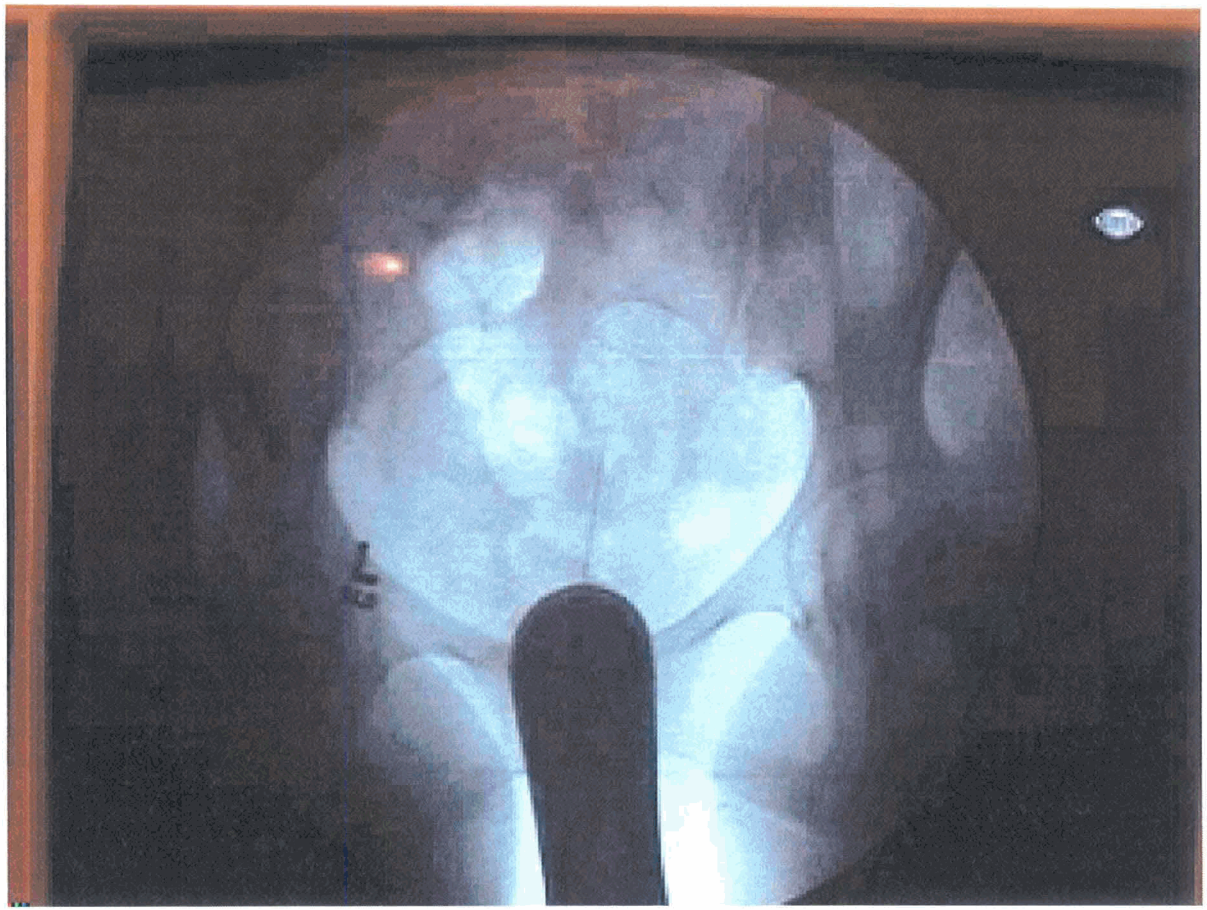
HSG-Anteverted Uterus Blocked Tubes



[Insert Video Clip: Blocked1]

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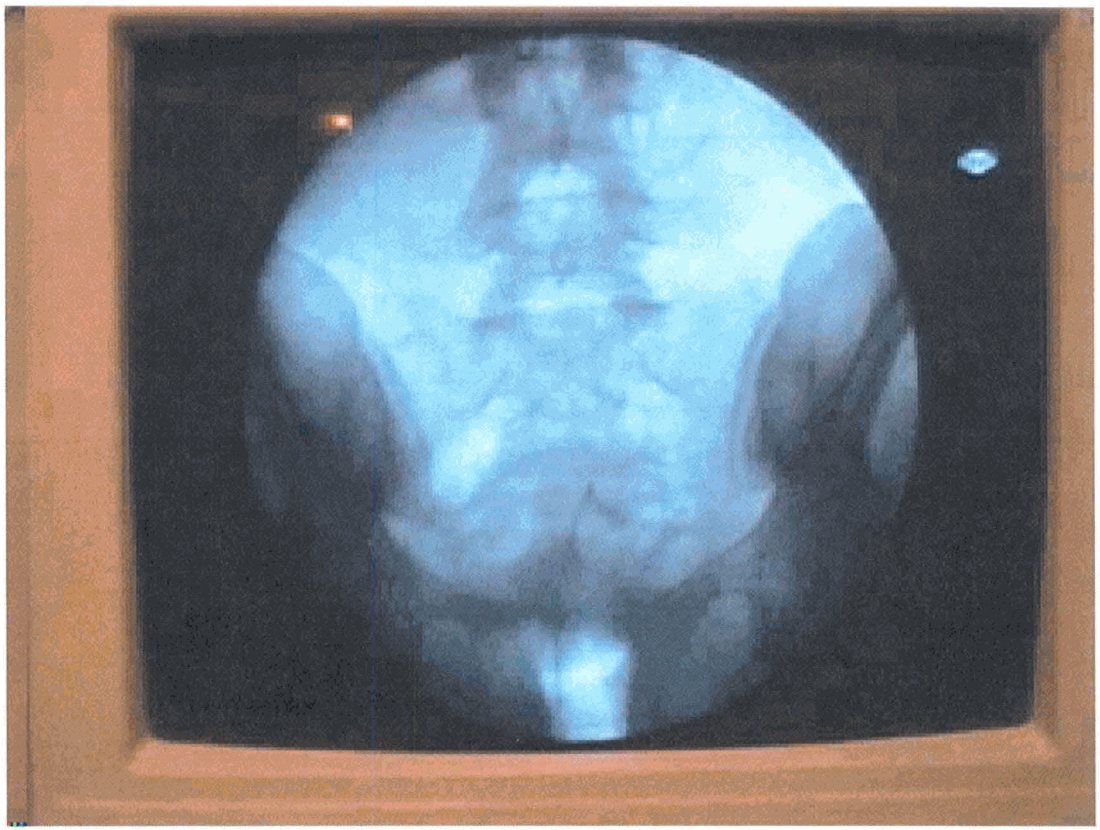
HSG-Retroverted Uterus Blocked Tubes



[Insert Video Clip Blocked2]

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HSG – Lessons Learned

- PHYSICIAN MUST REVIEW FILM IMAGES BEFORE MAKING A DETERMINATION
  - Impressions from 'real time' experience may be wrong
  - Additional resolution from film images may identify issues
  - Operator attention to patient issues or other areas of the image may cause mis-interpretation of fine features
- Patient must remain still when shooting films (except as required for rotation views)
- The cervical seal during contrast injection and remainder of the procedure is extremely important in order to maintain constant pressure throughout cavity

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HSG – Lessons Learned

- Lack of image quality on video display (and video ‘page prints’) may lead to misinterpretation.

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IX. POST-APPROVAL STUDY (PROPOSED)

7. EASE Clinical Trial Post Approval Study

The safety and effectiveness of the Adiana Transcervical Sterilization System has been assessed in a series of preclinical and clinical trials. The EASE clinical trial, a pivotal study, conducted to collect data to determine the safety and effectiveness of this device for permanent female sterilization, was filed under IDE G020172.

The EASE study was designed with a one year primary endpoint, and will follow all patients out to 5 years of reliance. At the time of the database freeze for this PMA (March 1, 2007) approximately one half (50%) of the total follow up in terms of 'woman-months' of reliance had been collected.

Thus the process of data collection related to the original trial cohort will continue.

Per Regulatory Guidance, *"Guidance for Industry and Staff – Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic Act,"* issued on April 25, 2006, Cytyc has developed the following specific question to be researched in a post-approval study.

- What are the 3, 4, and 5 year device failure/effectiveness rates?

To evaluate the 3, 4, and 5 year device failure/effectiveness rates, Cytyc will:

- Continue the current trial per IDE G020172 with yearly follow-up reporting out to 5 years.

All monitoring and data collection activities which occur during this follow-up period will be performed in accordance with the Good Clinical Practices which were employed throughout the EASE study. Any Serious Unanticipated Adverse Events will reported to FDA according to 21 CFR §812.150(b)(1). In addition, the results of this post-approval effort will be reported to FDA annually in Periodic Reports according to 21 CFR §812.150(b)(5).