PROTOCOL TITLE:
ATOM Study

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1.0 Study Summary

Study Title	**Assessment of Tubal Occlusion During Minimally Invasive Myomectomy (ATOM)**
Study Design	Single-arm prospective study
Primary Objective	Frequency of tubal occlusion in patients with fibroids immediately prior to and after completion of myomectomy
Secondary Objective(s)	● Tubal occlusion as compared to FIGO classification, size and anatomic location of fibroid(s) ● Rate of change in tubal patency after completion of myomectomy (occluded to patent or patent to occluded)
Research Intervention(s)/ Investigational Agent(s)	Chromopertubation immediately prior to and at completion of myomectomy with dilute methylene blue dye solution
IND/IDE #	N/A
Clinicaltrials.gov ID	
Study Population	Patients undergoing laparoscopic or robotic myomectomy by a Minimally Invasive Gynecologic Surgery provider at MedStar
Sample Size	Goal to enroll at least 50 patients
Study Duration for individual participants	Less than 10 minutes of additional operative time during previously scheduled surgery
Study Specific Abbreviations/ Definitions	Chromopertubation: an established procedure that involves injecting a dilute solution of medical-grade dye into the endometrial cavity and visualizing spillage of the dye through the fallopian tubes into the abdominal cavity, indicating patency of the tubes. Myomectomy: surgery to remove uterine fibroids Myoma/leiomyoma: synonym for uterine fibroid

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2.0 Objectives*

2.1 To evaluate the incidence of tubal occlusion in patients undergoing surgery for uterine fibroids before and after surgical intervention.

To assess the correlation between tubal patency and fibroid characteristics based on FIGO classification in patients undergoing surgery for uterine fibroids.

To assess characteristics of patients who have change in tubal occlusion

2.2 Tubal occlusion will be observed in patients with fibroids. The frequency of tubal occlusion will change after myomectomy compared to pre-myomectomy.

3.0 Background*

3.1 Fibroids have a prevalence >75%, making it the most common benign uterine disease [Zepiridis 2016, Lazaridis 2013, Giuliani 2020]. Fibroids are well known to contribute to infertility and early pregnancy loss [Don 2023, Pritts 2025, Carson 2021, Giuliani 2020]. This is typically thought to be secondary to distortion and impairment of the endometrial cavity or myometrial junction. However, it has been stressed in recent reviews that the full mechanism of the effect of fibroids on infertility is not fully understood, and more studies are needed [Donnez 2024]. It is theorized but not well confirmed through evidence-based studies that fibroids may also occlude or compress fallopian tubes and contribute to tubal occlusion that may contribute to infertility [Don 2023, Zepiridis 2016, Horne 2007, Somigliana 2021]. Additionally, up to 25-35% of female-factor infertility is related to tubal disease [ASRM Practice Committee 2021, Carson 2021, Mayrhofer 2022]. There is very little data on tubal patency assessment in patients undergoing myomectomy. A 2020 study compared frequency of tubal occlusion diagnosed by hysterosalpingogram to multiple variables, including fibroids, but was noted in subsequent reviews to be of poor quality and was specific to a low-resource setting in Cameroon [Egbe 2020, Somigliana 2021]. We have been able to identify only one prospective study from 1993 that specifically evaluated fallopian tube filling during post-myomectomy hysterosalpingogram, though the primary outcome of this study was endometrial cavity architecture [Lev-Toaff 1993]. A recent case report of removal of a particularly complex broad ligament fibroid describes the use of postoperative hysterosalpingogram, but did not utilize intraoperative chromopertubation [Sankey-Thomas 2024]. While this protocol may

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be performed anecdotally in practice, empirical evidence for tubal evaluation before and after myomectomy is lacking.

Chromopertubation under direct laparoscopic visualization is considered the "gold standard" for evaluation of tubal patency [Mayrhofer 2022, Mayrhofer 2024, Nako 2024, Saunders 2011, Carson 2021, ASRM Practice Committee 2021]. This is typically accomplished with dilute methylene blue or indigo carmine dye [Mayrhofer 2024].

3.2 Two recent retrospective studies have demonstrated a significant association between presence of leiomyoma and tubal occlusion in women with infertility [Mayrhofr 2024, Nako 2024]. Nako et al (2024) found a significant association only with submucosal fibroids. We have not identified any recent prospective studies evaluating tubal patency in patients with uterine leiomyoma or those undergoing myomectomy. Mayrhofr et al acknowledged this deficit in their 2024 retrospective study, stating that there is a "need for more studies on tubal patency epidemiology" and ultimately that "women with subfertility should undergo tubal patency testing early during infertility evaluation in order to not delay further treatment, particularly women with hydrosalpinges and myomas, as those were found to have the highest risk for occlusion." In particular, the mechanism of proximal tubal occlusion is not yet well understood [Mayrhofer 2024]. Somigliana et al (2021) also emphasize that more studies on the effects of fibroids on natural fertility are "urgently needed."

A systematic review of the effects of fibroids on fertility found that only submucosal fibroids had a negative effect on fertility. However, that study did not specifically evaluate tubal patency, only included patients with diagnosed infertility, and did acknowledge that evidence for removal of intramural fibroids was of poor quality and further studies are needed [Pritts 2025]. Don et al (2023) acknowledge that more studies are needed on the effect of myomectomy on tubal function.

3.3 Most data regarding tubal patency assessment are collected on patients already diagnosed with infertility, which introduces the possibility of multiple confounding variables. There are no recent prospective studies of tubal occlusion in patients with fibroids or patients undergoing myomectomy.

Earlier detection of tubal disease may allow for a quicker and more proactive work up and counseling before other factors such as age and oocyte quality further impact fertility options. There is also limited data on tubal occlusion or patency in patients with fibroids and those undergoing myomectomy. Underappreciation of the effect of uterine fibroids and myomectomy on tubal patency and

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subsequent delays in diagnosis could further complicate fertility due to age, reduced ovarian reserve and oocyte quality. Knowledge of tubal occlusion may influence referral to an infertility specialist or counseling for ectopic pregnancy risk.

This proposed study can help contribute to a more proactive approach to early detection and intervention for tubal occlusion in a high-risk patient population in order to achieve the following goals: to improve understanding of the effects of fibroids and myomectomy on tubal occlusion and to gain a better understanding in order to inform future studies to optimize counseling, diagnosis, and early intervention for tubal occlusive disease

4.0 Study Endpoints*

4.1 Patient enrollment from time of IRB approval until April 2026 with goal of enrolling at least 50 patients

5.0 Study Intervention/Investigational Agent

5.1 Intervention: Chromopertubation, an established medical procedure used to evaluate fallopian tubal patency and infertility, will be performed immediately prior to and at completion of minimally invasive gynecologic surgery for fibroid removal (myomectomy). This procedure uses a solution of dilute methylene blue dye injected into the uterine cavity.

5.2 Drug/Device Handling: no investigational drugs or devices are being used. Storage and handling of methylene blue dye and normal saline will be performed according to existing hospital protocols.

5.3 N/A – No IND

6.0 Procedures Involved*

6.1 This is a single-arm prospective study using chromopertubation to assess tubal occlusion in patients undergoing minimally invasive gynecologic surgery for uterine fibroids. This procedure involves injecting a dilute solution of medical-grade dye into the endometrial cavity and visualizing spillage of the dye through the fallopian tubes into the abdominal cavity, indicating patency of the tubes that would allow for spontaneous conception. Chromopertubation will be performed at the initiation and completion of the surgery and tubal occlusion will be documented.

6.2 Chromopertubation procedure:

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- Pre-surgery: chromopertubation will be performed at the start of laparoscopic or robotic surgical procedure, once abdominal ports are in place and uterine manipulator placement has been performed prior to initiation of any myomectomy or other interventional surgical procedures.

- Post-surgery: Chromopertubation will again be performed at the end of the surgery, once all surgical interventions are complete and prior to removal of abdominal ports and uterine manipulator.

- Chromopertubation will be performed per standard clinical protocol as follows: Up to 50 mL of dilute methylene blue dye solution (1mL of 10 mg/mL 1% methylene blue in 200 mL normal saline) will be injected into the uterine cavity through a uterine manipulator with a patent central channel. This dose totals up to 2.5 mg of dilute methylene blue dye per chromopertubation injection and an anticipated maximum dose of 5 mg of dilute methylene blue per patient. Spillage of dye should be visible immediately after injection of dilute dye into the endometrial cavity if tubes are patent.

Adverse event monitoring:

- As chromopertubation is an established medical procedure, patients will be monitored according to the standard intra-operative and post-operative criteria. If there are any signs of adverse events prior to completion of the study interventions, the study procedure will be aborted immediately and supportive therapy provided as needed. This will be done through communication between the surgical and anesthesiology teams.

- Patients will be observed in the post-anesthesia care unit (PACU) according to standard postoperative protocol for any adverse events. In accordance with our standard post-operative practice, all patients will be discharged home upon meeting standard postoperative discharge criteria. As per routine standard protocol, all patients will be called at home to assess for any issues or concerns and to see how they are doing overall. This call is performed by either the attending surgeon or fellow on post-operative day #1, if discharged after surgery, or rounded on if admitted to the hospital overnight.

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- Patients who report adverse effects once at home will be triaged and evaluated according to standard post-operative precautions.

- All patients will be monitored according to standard protocol for any intra-operative or post-operative adverse events.
- The following medical supplies, drugs, and devices will be used:
    - The only components that will be used during this study that are exclusive to the investigation is the dilute methylene blue dye solution in normal saline. This is an approved medical dye that is commonly used for a variety of medical and surgical procedures and is administered via various routes (intravenous, instillation into bladder, uterus, etc.). No use during this study will be outside the standard usage protocol.
    - No additional medical devices outside of what is standard for the planned surgical procedure will be utilized for investigational purposes. The application of the methylene blue dye solution can be performed using the uterine manipulator that is already a standard instrument used during the surgical procedure.
- Source records include the patient chart - including demographic data, medical and surgical history, radiologic imaging, clinical notes, and operative reports.

6.3 The following data will be collected:

- *From chart review:*
    - Age
    - Obstetric history
    - Gynecologic history
    - Preoperative imaging findings

During study procedures intra-operatively:

- Preoperative tubal patency or occlusion - unilateral vs bilateral, proximal vs distal
- Postoperative tubal patency or occlusion - unilateral vs bilateral, proximal vs distal
- Size, anatomic location and FIGO classification of fibroids removed

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6.4 There are no plans for long-term follow up at this time. Any additional planned contact with study participants for research purposes will be submitted to the IRB through a protocol addendum.

7.0 Data and Specimen Banking*

7.1 No specimens will be obtained. Data will be stored on the secured institutional OneDrive.

8.0 Sharing of Results with Subjects*

8.1 As this study is not blinded, the patient may inquire about the results at any time. Results will be noted in the operative report.

As no standard guidelines exist, patients for whom bilateral tubal occlusion was observed will be counseled of the following options for future tubal disease testing:

(1) Outpatient tubal patency assessment at either 3 months after surgery or once pregnancy is desired if more than 3 months after surgery. The minimum recommended interval between myomectomy and conception is 3 months to allow for myometrial healing.

(2) Referral to a reproductive endocrinology and infertility specialist

In the case of unilateral occlusion, standard clinical counseling for unilateral tubal impairment or absence will be provided.

9.0 Study Timelines*

- The estimated date for the investigators to complete this study:
  - May 2025: Begin patient enrollment/data collection
  - April 2026: complete data collection, begin analysis
-

10.0 Inclusion and Exclusion Criteria*

10.1 A HIPAA waiver was requested in order to enable trained IRB approved study team members to screen provider schedules and EMR patient charts for patients who meet study criteria.

10.2 **Inclusion criteria:**

- Patients over age 18 who are undergoing minimally invasive uterine-preserving gynecologic surgery for removal of uterine fibroids (myomectomy) by a minimally invasive gynecologic surgeon at MedStar.

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Exclusion criteria:

- Patients with both fallopian tubes absent
- Patients in whom it is not possible to place a uterine manipulator or catheter
- Patient with known tubal disease or occlusion, or patients who have undergone prior tubal surgery
- Patients with allergy to methylene blue dye or G6PD deficiency
- Patients with positive pregnancy test on day of surgery

10.3 The following special populations will **not** be included:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

11.0 Vulnerable Populations*

11.1 N/A

12.0 Local Number of Subjects

12.1 We anticipate enrolling a minimum of 50 patients

13.0 Recruitment Methods

13.1 A member of the research team will reach out to the eligible patients for recruitment and consent. This may be done in person, via telehealth, or via phone call.

13.2 The schedules of surgeons in the department of Minimally Invasive Gynecologic Surgery will be reviewed by a member of the research team and patients will be screened for inclusion criteria in this research study. A HIPAA waiver to review patient charts is requested for screening purposes.

14.0 Withdrawal of Subjects*

14.1 Subjects will be withdrawn without their consent under the following circumstances: the planned myomectomy is aborted for any reason, the subject demonstrates an adverse reaction to the methylene blue dye, or there are complications in the operating room for any reason that result in inability to safely complete the procedure.

14.2 N/A

14.3 This study includes a one-time intervention. No further data will be collected if a participant withdraws from study participation. Partial withdrawal is not applicable.

15.0 Risks to Subjects*

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Risks of Methylene Blue intrauterine instillation: low risk with rare risk of adverse events

Use of sterile dilute methylene blue dye installation in the uterus and fallopian tubes is routine for performing chromopertubation and is widely considered safe and low risk. In addition to intrauterine injection, methylene blue dye is routinely used in solution to fill the bladder and check for injury, injected intravenously to evaluate ureteral patency during urinary excretion, and injected directly into tissue for sentinel lymph node identification [Bezu 2010, Ramin 2011, Barbieri 2014]. Methylene blue dye has been safely used to perform chromopertubation since first introduced in 1968 [Ansari 1968].

There are reports of rare allergic reactions, including urticaria, anaphylaxis and pulmonary edema, to methylene blue dye. Another rare potential adverse effect is methemoglobinemia, which occurs when methylene is given in high doses or in patients with G6PD deficiency [Jena 2019, Bagadia 2017]. The maximum safe dosage is considered to be 7 mg/kg [Jena 2019, Bagadia 2017]. Several case studies of adverse effects are related to direct tissue injection of non-dilute methylene blue dye, though reports of reactions after chromopertubation have been described [Akazawa 2019, Rzymski 2023]. Our protocol will use an approximate total dose of 5 mg methylene blue dye in dilute solution, a low dose that is considered safe from systemic side effects [Barbieri 2014].

Chromopertubation procedure: low risk

Most risks of chromopertubation as compared to other methods of tubal patency assessment are the general and universal risks of undergoing surgery. However, in our study population, all patients are already undergoing medically-indicated surgery under general anesthesia for treatment and management of gynecologic pathology. Participation in this study for tubal assessment will not incur additional risks related specifically to surgery other than adding an estimated additional operative time of less than 10 minutes. Chromopertubation can typically be performed in 1-2 minutes.

Other risks include emotional distress due to the results of the chromopertubation procedure and potential concerns about fertility.

As with all studies that include access to PHI, there is a low risk of breach of confidentiality.

15.1 As the study intervention is an established and commonly performed medical procedure, it is not thought to carry unforeseeable risks.

15.2 N/A

15.3 Concerns about tubal disease and fertility associated with this study may confer stress onto the partners of study subjects.

16.0 Potential Benefits to Subjects*

16.1 Patients participating in this study will receive a gold-standard evaluation of tubal patency concurrently during surgery. For patients for whom tubal patency assessment would be indicated or desired, this study would avoid radiation exposure and discomfort during outpatient hysterosalpingogram. This evaluation may or may not be clinically relevant to an individual patient's fertility or desired family planning outcomes.

16.2 We cannot guarantee that there will be an immediate or long-term benefit to individual patients participating in the study.

17.0 Data Management* and Confidentiality

17.1 Data containing PHI will be kept confidential in a Microsoft Excel document stored in an electronic, password protected drive located on the institutional OneDrive. This database will be accessible only to IRB approved study team members. The data will be destroyed following study completion as per institutional requirements for human subject research.

A de-identified database will be provided to the statistical team for data analysis.

Consent forms will be available on paper and electronically. All electronic consent forms will be stored in a secure database for the duration of the study. Paper consent forms will be stored in a locked office for the duration of the study and then destroyed in accordance with PHI requirements.

17.2 No specimens will be collected. Data will be handled as noted above in section 17.2.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

18.1 N/A. See sections 6.2 and 7.1

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 In order to protect subjects' privacy interests, subjects will only interact with or provide personal information to members of the research team designated on the IRB during study introduction, recruitment, and consent. Otherwise, subjects will have standard interaction with their surgeon and the medical and surgical teams participating in their care.

19.2 Subjects will be introduced to the research study once they have a definitive surgical plan. They will be assured that the study interventions include an established and commonly performed

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surgical procedure and that no unapproved agents or protocols will be utilized. They will be informed that the study does not include any blinding or randomization, and they have the choice to request their results at any time. They may communicate directly and openly about the study with the members of the research team, including their surgeon.

19.3 A HIPAA waiver is requested to screen patient charts for those meeting inclusion criteria on the surgeons' EMR schedules. Subjects will be enrolled and consented before any additional information is collected. Members of the research team will collect data from chart review both before and after the study interventions.

20.0 Compensation for Research-Related Injury

20.1 N/A

21.0 Economic Burden to Subjects

21.1 N/A

22.0 Consent Process

22.1 We will be obtaining consent from all subjects enrolled in the study. Consent will only be obtained from English-speaking adults who are able to provide consent. A study team member will contact the potential participants by either phone, remote telehealth visit, or meet in person to discuss the study and answer all questions. Potential participants may elect to defer signing consent if they wish to take additional time to consider whether to enroll. During the recruitment process both the clinical providers and the research study team members will explain that participation will in no way affect the patient's clinical care. Patients will be offered a paper or electronic consent to review. Electronic consents will be sent using the Interlace eConsent platform. During the consent process, the research team member obtaining consent will review the entire consent form with the patient, answer any/all questions to help ensure that the patient understands the steps involved in participation, and ask for understanding throughout the process to help ensure comprehension. After the consent form has been completely reviewed and the study process explained in full, if the patient reports they understand the consent form and elects to participate in the study, then consent will be obtained by electronic or written consent. Consent may be obtained by any of the persons listed on the IRB application, which may include the attending surgeon, fellow, or student member of the research team.

Once identified as potentially eligible to participate a member of the research team will contact the patient to further discuss the study and

answer questions using a standard process. If the patient chooses to enroll, they will be consented. Consent may be obtained electronically or in person. Once the consent is completed and eligibility is confirmed, participants will be enrolled in the study.

If patients are not scheduled for a formal in-person visit, patients will be introduced to the study and consented prior to surgery in the pre-operative area. Patients will be provided a copy of the signed study consent. Consent forms will be scanned or uploaded into the patient chart.

Non-English Speaking Subjects

- *N/A*

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- N/A

Subjects who are not yet adults (infants, children, teenagers)

- N/A

Cognitively Impaired Adults

- *N/A*

Adults Unable to Consent

- *N/A*

23.0 Process to Document Consent in Writing

23.1 A written consent document will be used

24.0 HIPAA Authorization

24. Request for a Waiver of HIPAA Authorization: regardless of IRB review category, for a chart review study involving Protected Health Information (PHI) a Waiver of HIPAA Authorization for the use or disclosure of PHI needs to be requested and obtained. The following elements from 45 CFR 164.512 (i) (1) (i) must be met for the IRB to waive the requirement:

24.1 A waiver of HIPAA authorization is being requested solely for the purposes of screening patient charts and contacting patients for potential enrollment in this research study. All subsequent research activities will be performed with patient consent.

24.1.1 The use or disclosure of protected health information during the screening and recruitment process of the research involves no more than minimal risk to privacy of individuals.

25.0 Setting

25.1 Research will be conducted at MedStar Health facilities. Screening and recruitment will be conducted at outpatient office locations used by minimally invasive gynecologic surgeons. Study interventions and procedures will be performed in MedStar hospital operating rooms.

26.0 Resources Available

26.1 This research will be conducted within the department of Minimally Invasive Gynecologic Surgery and will have access to the facilities, research staff, surgeons, and fellows in this department. Research assistance will be provided by students at Georgetown University School of Medicine, who are listed on the IRB application.

- Funding for supplies will be provided by the institution.
- The facilities for the study interventions will be the MedStar hospital operating rooms. Subjects will have access to ongoing follow up care by their surgeon.
- All persons on the research team will be IRB-approved.

27.0 Multi-Site Research*

27.1 N/A

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