

STUDY TITLE: The Use of Low Dose Metronidazole to Decrease Postoperative Pain After Endometriosis Surgery: A Prospective, Randomized, Placebo-Controlled Trial

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Principal investigator: Resad Pasic, MD, PhD

Title of the Research Project

The Use of Low Dose Metronidazole to Decrease Postoperative Pain after Endometriosis Surgery: A Prospective, Randomized, Placebo-Controlled Trial

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1. Background/Problem Statement:

Endometriosis is a chronic inflammatory condition involving endometrial-like tissue outside the uterus affecting approximately 1 in 10 reproductive age women (1). Endometriosis often presents with symptoms of abdominal pain, dysmenorrhea, dyspareunia, dyschezia, infertility, but it may be asymptomatic (2). It is found in up to 50% and 87% of women with infertility and chronic pelvic pain, respectively (3). Laparoscopic excision management can significantly improve pain symptoms in 62-80% of patients with endometriosis (4)(5). Treatment for patients who continue to have pain symptoms despite surgical excision is limited, especially in patients with pregnancy wishes who wish to avoid hormonal therapy. Given the refractory nature of the disease and its morbidity, it is estimated that the yearly costs of endometriosis treatment exceeds \$ 22 billion in the United States alone based on data from 2002 (9). Recent publications suggest a link between dysbiosis, an imbalance in the microbiome, and endometriosis (7, 8, 10, 11, 14, 15).

The microbiota communicate with and modulate the host immune system and it has been associated with inflammatory bowel disease, endometrial, ovarian, and colorectal cancer (10) (11). Recent studies reveal an association between dysbiosis in patients with endometriosis and surgically induced endometriosis murine models with significant increases in *Streptococcaceae*, *Staphylococcaceae*, *E. Coli*, *Mollicutes*, *Shigella*, *Actinobacteria*, *Enterobacteriaceae*, *Peptococcaceae*, *Betaproteobacteria*, and a decrease in *Lactobacillaceae* (7).

The gut microbiota has also been implicated in pain processes originating in the gut (12). The microbes in the intestine are involved in the production of neuroactive metabolites such as gamma-aminobutyric

acid (GABA), serotonin, norepinephrine, and dopamine (12). GABA has been shown to have an inhibitory effect on nociceptive transmission by depolarizing GABA receptors expressed by peripheral dorsal root ganglia neurons connected to the spinal cord (13). In addition, around 95% of the serotonin (5-HT) in the body is contained within the gut and can be synthesized by *Candida spp.*, *Streptococcus spp.*, *Escherichia spp.*, and *Enterococcus spp.* 5-HT acts primarily as a pain-inducing mediator, regulator of GI motility, secretion, and sensory perception (12, 13).

In a cohort study by Glick et al, patients with a similar chronic inflammatory disorder, Crohn's disease, recovering from ileal resections who received low dose metronidazole for 3 months had clinically significant decreases in colonoscopic recurrences at 1 year (15). The use of low dose metronidazole in their study was associated with relatively low adverse events, and low drop out rates, than seen in studies using prolonged higher doses of metronidazole for Crohn's disease.

The microbiome has been shown to alter estrogen metabolism, increasing estrogen levels in women with dysbiosis, by favoring reuptake of estrogen previously destined to be excreted in the feces (6). Given the role of estrogen in the growth of endometriosis lesions, decreasing levels of these pathogenic bacteria may significantly limit the progression of endometriosis.

Furthermore, fertility outcomes of patients undergoing IVF have also been shown to be affected depending on microbes present in follicular fluid (14). Pelzer et al, found that the follicular fluid harboring certain opportunistic pathogens was associated with poor IVF outcomes including decreased embryo transfer rates and decreased pregnancy rates (14).

Finally, an animal model showed the effectiveness of metronidazole alone in significantly reducing the size of endometriosis lesions (8). The same study showed that lesion growth was re-established in mice gavaged with faeces from mice with endometriosis, after initial treatment with metronidazole, suggesting that the microbiome may be involved in endometriosis development (8).

Hypothesis:

In a randomized study of participants who are diagnosed with endometriosis surgically, treatment with low dose oral metronidazole will significantly decrease subjectively reported pain postoperatively when compared to participants receiving placebo.

2. Objectives:

The purpose of this study is to determine a difference in participant reported pain after endometriosis surgery in participants given oral metronidazole versus placebo.

3. Study Design/Methodology:

The study is a prospective, randomized, placebo-controlled trial. Investigators and participants will be blinded as to whether the participant is in the metronidazole or control arm. The placebo drug will not be matched in appearance to metronidazole. A blinding plan with instructions to investigators and pharmacy will be provided to keep details of study drug and placebo from study participants.

A total of 90 participants will be required for the study. The metronidazole arm will have 45 participants and the control arm will have 45 participants. This is based on the primary outcome of binary, self-reported pain persistence at the 6 week follow-up. Assuming a 10% pain persistence in the metronidazole group and a 40% pain persistence in control arm, we require $n=36$ participants per group to have a 80% power to detect a significant difference between groups with Fisher test at a significance level of $\alpha=0.05$. Assuming a 20% drop-out rate, we randomize 45 participants per group to ensure 36 with collected information at 6 weeks out. Sample size calculation was performed in G*Power, version 3.1.9.2.

Expected duration of the study is 18 months for participant recruitment plus 60 months for data collection.

Intervention drug:

Metronidazole 250mg tablet orally three times a day for 14 days vs.

Halal and Kosher certified gelatin placebo capsules orally three times a day for 14 days

Withdrawal criteria:

Participant requests terminating participation

Serious adverse events that would pose increased risk to subject's safety including but not limited to neurological symptoms.

Inclusion criteria:

- Able to give informed consent
- Women aged 18-50 years old
- Scheduled to undergo excision of endometriosis
- Able to read and write in English and or Spanish
- Pain score > 2 on a 10 point visual analogue scale at baseline
- Negative screening by CAGE questionnaire

Exclusion:

- Refusal to surgery
- Contraindication to surgery
- Known allergy to metronidazole
- Known allergy to any component in gelatin placebo capsules
- Scheduled hysterectomy
- Endometriosis excision surgery within the last 3 months
- Elevated serum creatinine
- Abnormal liver function test greater than 2 times the normal
- Current pregnancy
- Breastfeeding
- Use of Disulfiram within the last 2 weeks
- History of Cockayne syndrome
- Inability to abstain from alcohol during the use of study drug

Participants who have visual evidence of endometriosis intraoperatively will be randomized to the metronidazole plus routine postoperative care arm or the placebo plus routine postoperative care arm using the Redcap stratified

randomization tool. A clinician involved in the participant's surgical care but not involved in the study will perform the randomization. Metronidazole and placebo will be prepared and dispensed by the University of Louisville pharmacy per the randomization. A blinding plan will be provided to the University of Louisville pharmacy with instructions to keep participants and investigators blinded to details about drug dispensed. All investigators with the exception of Cathy Whalen, PharmD will be blinded. Cathy Whalen will be able to proceed with unblinding in the event unblinding needs to occur for any participants prior to completion of the study. Participants will start the medication within a week of surgery. Participants will receive a medication diary and be asked to document any adverse events and all medications taken until 6 weeks postoperatively. The medication diary will be reviewed by investigators at the postoperative clinical visits. The study participants will return to the clinic for routine post operative care at 2 weeks, 6 weeks, 12 months, 24 months, 36 months, 48 months, and 60 months postoperatively. Investigators will email the participants, via Redcap software, a survey (Appendix II) at the time of each routine clinical visit and at 6 months postoperative, with the exception of the 2 week postoperative visit. In the event the participant lacks computer access participants will be mailed a paper version of the survey with return postage and this will be entered into Redcap by one of the investigators.

Clinical evaluations:

All participants interested in the study will have a history and physical prior to enrollment including a review of concomitant medications and alcohol dependence screening with the validated CAGE questionnaire.

Baseline participant demographics, and procedural data will be collected and entered in Redcap (Appendix I, III).

Participant will complete the following at baseline and each postoperative visit listed above:

1. Intensity of pain in domains such as dysmenorrhea, dyspareunia, dysuria, dyschezia, and non-menstrual pelvic pain will be recorded via the visual analog scale (Appendix I, II), a validated and reliable method for measuring endometriosis associated pelvic pain
2. Quality of life will be measured by the validated Endometriosis Health Profile, the short-form version, EHP-5 (ATTACHMENT I)
 - a. For EHP-5+6, the 11-item responses were summed and transformed according to the EHP-5

manual on a scale from 100 (worst possible HrQoL) to 0 (best possible HrQoL)

3. Sexual health will be measured via the validated female sexual function index, FSFI (ATTACHMENT II)
 - a. FSFI total score variable was the most predictive classification variable. Specifically, they concluded that scores of 26.55 most accurately captured clinically relevant sexual dysfunction.
 - b. one indication that the FSFI has been scored incorrectly is a total score falling outside of the possible range of 36
 - c. Score of 0 indicates that participant did not have any sexual activity in the last 4 weeks.
4. Data on pregnancy wishes and postoperative pregnancies will be collected (Appendix I, II)

Surgeons involved in the study will operate at two hospitals, University of Louisville Hospital and Norton Hospital. They will complete a detailed record of intraoperative findings, surgical procedures performed, stage of endometriosis based on the revised American Society of Reproductive Medicine classification, intraoperative and postoperative complications (Appendix III). A separate IRB approval will be obtained from Norton Hospital prior to enrolling patients at their clinical site.

Only the investigators listed in this study will collect participant information and store all data within the encrypted database Redcap through the secure University of Louisville sponsored intranet. The data will be also stored in an Excel worksheet accessed through the University of Louisville's secure intranet in order to perform cross checks of the data in Redcap.

5. Subject Recruitment Methods:

Women scheduled for endometriosis excision surgery at the University of Louisville Hospital's minimally invasive gynecologic surgery clinic, gynecologic oncology clinic, and Norton hospital women's care clinic between 18-50 years of age will be invited to participate in the study. Participants who meet inclusion criteria will be consented at the time of their preoperative visit or on the day of their surgery by one of the physician investigators listed on this document.

Participants who complete the 6 week and 5 year postoperative survey, and wish to be included, will be entered into two drawings to receive a \$100 Visa

branded U of L card through the University of Louisville's sponsored Swift Prepaid system. We will obtain sensitive personal information, including but not limited to the participant's social security number, from the two participants who obtain the \$100 Visa branded U of L card. Personal information will be stored in a secure excel document accessed only through the University of Louisville Hospital's intranet. Participants who wish to forgo the drawing, but meet inclusion criteria, may still participate in the study protocol. No one participant will be able to win the drawing twice.

6. Informed Consent Process/Complete Waiver Process:

All participants who agree to enroll in the study after meeting inclusion criteria will be consented using a written informed consent form and a HIPAA consent form at the time of the preoperative visit or on the day of surgery. Participants will be randomized to the intervention postoperatively once intraoperative evidence of endometriosis is confirmed. Only the clinical investigators named on this protocol will consent the participants for the trial. Spanish speaking participants will be consented using a translator and they will be provided with translated study surveys verified by the University of Louisville Hospital's language department.

7. Research Procedures:

Aside from randomization to oral metronidazole plus routine postoperative care vs. placebo plus routine postoperative care, no procedure will be performed for study purposes that would not normally be performed during clinical evaluation and surgical care of the participant.

Participants will be randomized to metronidazole 250 mg orally three times a day for 14 days postoperatively with routine postoperative care or placebo orally three times a day for 14 days plus routine postoperative care.

8. Minimizing Risks:

Participants will have data collected in the Redcap and Excel software within the University of Louisville's protected intranet server. Participant data will only be

accessed through the secure University of Louisville intranet by the investigators. Any paper data collection forms will be stored in a locked filing cabinet file in the minimally invasive gynecology clinic at the University of Louisville. Paper data will be destroyed in a HIPAA compliant manner at the end of the study. Any adverse events will be reported immediately to the principal investigator (PI). A medication diary will be collected at the 2 week and 6 week postoperative visit and reviewed by the investigators for adverse events and compliance. All adverse events will be followed until resolution. Neurological symptoms and other serious adverse events that would pose an increased risk to the subject's safety will result in patient withdrawal from the study. Adverse events will be reported as described in the University of Louisville Human Subjects Protection Program Policy Manual Section 7.10. Research pharmacist Cathy Whalen will have access to the participant's study arm and will provide investigators with ability to unblind participants at completion of the study and or in the event of a serious adverse event. Participants will be provided with the phone number of the clinic and PI and will be instructed to contact the clinic and/or PI should they have any questions or problems.

9. Plan for Analysis of Results:

Demographics and baseline clinical characteristics will be compared between the metronidazole group plus routine postoperative care and placebo group using counts, proportions, and chi-squared/Fisher test for categorical variables and means, standard deviations and t-test for continuous variables. The outcome of binary, subject pain persistence at each measurement occasion will be compared between groups using the Fisher exact test. Multivariate logistic modeling will be considered to control for confounders after randomization, if any, and other meaningful predictors (such as baseline pain) in addition to the MZT effect. Logistic longitudinal growth models may be used to model the entire course of the binary pain persistence across the measurement occasions (6 weeks, 12 months, etc.) A continuous VAS pain score will also be obtained and compared between groups using a t-test at each time point. Multiple linear regression may be used to adjust for confounders, and linear growth models used to jointly model the trajectory of VAS pain score across the study period. Transformations (such as logarithmic) and/or non-parametric analyses may be utilized as needed. All analyses were performed using R statistical software.

10. Research Materials, Records, and Privacy:

Data will be collected directly from participants utilizing surveys as well as the medical record. We will be recording data from the medication diary and survey listed in Appendix I, II, and III.

Data collected from participants will allow determination of efficacy of low dose metronidazole in the postoperative period in domains such as pain, fertility, quality of life, and sexual health.

The data collection forms will be stored in a locked cabinet file at the University of Louisville minimally invasive gynecologic clinic and the electronic database created from the data collection forms will be saved in the password encrypted University of Louisville intranet Excel worksheet and Redcap software.

At the study completion, all personal identifiers will be destroyed in the HIPAA compliant manner. Access to data collected will be exclusively available to the investigators listed on this document.

All institutional and Federal regulations concerning the Informed consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

11. Funding:

Self funding

12. References

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associated with minimal, mild, and moderate endometriosis. *Fertil Steril*. 1994; 62:696-700. PubMed ID: 7926075

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APPENDIX I: (Questions below will be available on Redcap for participants to fill out via an online survey)

The Use of Low Dose Metronidazole to Decrease Postoperative Pain After Endometriosis Surgery: A Prospective, Randomized, Placebo-Controlled Trial

The purpose of this questionnaire is to measure if treating patients with oral metronidazole will improve short and long term pain.

The questionnaire will involve questions about your pain, pregnancies, fertility, sexual health, and quality of life.

Approximate duration of questionnaire is 20 minutes.

BACKGROUND INFORMATION:

Record number: _____

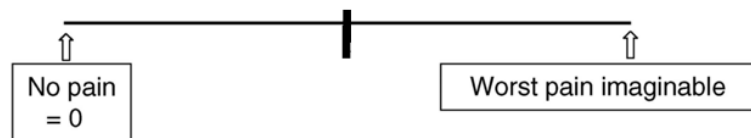
First and Last Name: _____

Date of birth: _____

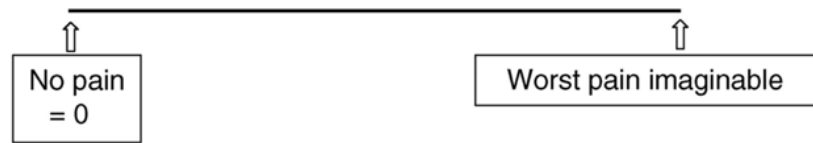
Age (years): _____

Please place a vertical mark on the line below to indicate the level of pain

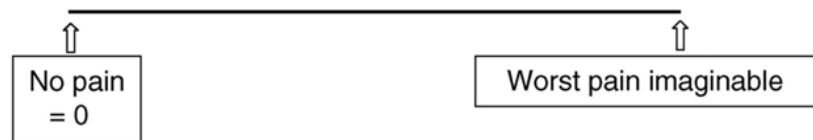
Example: How would you rate your overall pain in scale below?



A. How would you rate your **overall pain in the lower abdomen** on the scale below:



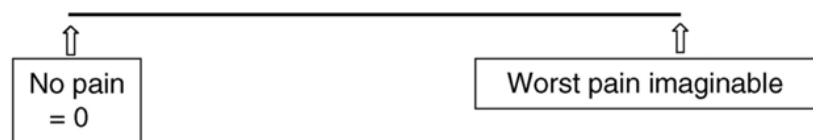
B. How would you rate your pain in the **lower abdomen during your periods** on the scale below?



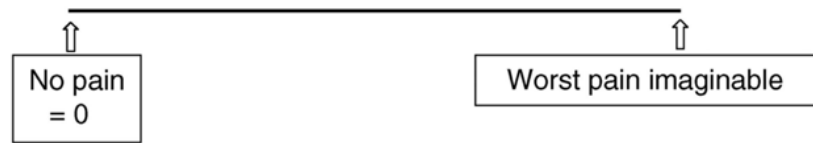
C. How would you rate your pain in the **lower abdomen between your periods** on the scale below?



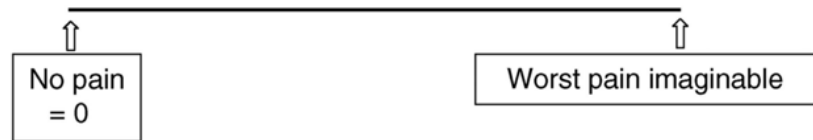
D. How would you rate your **pain during a bowel movement, especially during your periods**, on the scale below?



E. How would you rate the **pain when you urinate, especially during your periods**, on the scale below?



F. How would you rate your **pain with deep penetration during sex**, on the scale below?



ENDOMETRIOSIS HISTORY:

Please circle or write in responses

1. What is your race/ethnicity?
 - a. Asian/Pacific Islander
 - b. American Indian/Alaskan Native
 - c. Black non-Hispanic

- d. Black Hispanic
- e. Hispanic
- f. White non-Hispanic
- g. I don't know
- h. Other: _____
- i. Decline to answer

2. How old were you when you were diagnosed with endometriosis?

3. How many years ago did your pelvic pain symptoms start? Circle one option below

- A. Less than 1 year ago
- B. 1-5 years ago
- C. 6-10 years ago
- D. 11-20 years ago
- E. More than 20 years ago
- F. I don't know

4. Are you currently taking a birth control/hormonal medication?

- A. YES
- B. NO

IF you answered YES to question 4, please circle contraceptive/hormone that you currently use:

- A. Combination oral birth control
- B. Progestin only pills
- C. Nuvaring

- D. Birth control patch
- E. Lupron (leuprolide) injection
- F. Depo Provera injection
- G. Orlissa pill
- H. Other: _____
- I. I don't know

5. Do you wish to get pregnant within the next year?

- A. YES
- B. NO
- C. I don't know

6. Have you ever been diagnosed with infertility?

- A. YES
- B. NO
- C. I don't know

IF you answered NO or I DON'T KNOW to question 6, In the past or currently, have you had difficulty for at least a year in getting pregnant with a partner while actively trying?

- A. YES

- B. NO
- C. I don't know

7. Have you had any infertility treatments in the past?

- A. YES
- B. NO
- C. I don't know

IF you answered YES to question 7 please circle all treatments you have received?

- A. IVF
- B. Clomid
- C. Letrozole
- D. Intrauterine insemination
- E. Injectable hormones
- F. Other: _____
- G. I don't know

8. How many surgeries have you had for endometriosis in the past?

- A. 0
- B. 1
- C. 2
- D. 3 or more
- E. I don't know

9. Have you had endometriosis surgery in the last 3 months?

- A. YES

B. NO

Please fill out questionnaire EHP-5 (see attachment I)

Please fill out questionnaire Female sexual function index (see attachment II)

APPENDIX II (Questions below will be available on Redcap as an online survey for participants)

The Use of Low Dose Metronidazole to Decrease Postoperative Pain After Endometriosis Surgery: A Prospective, Randomized, Placebo-Controlled Trial

The purpose of this questionnaire is to measure if treating patients with oral metronidazole will improve short and long term pain.

The questionnaire will involve questions about your pain, pregnancies, fertility, sexual health, and quality of life.

Approximate duration of questionnaire is 20 minutes.

Record number: _____

First and Last Name: _____

Date of birth: _____

Age (years): _____

1. Since your surgery, have you noticed any improvement in the **overall pain in your lower abdomen?**

a. YES

b. NO

IF you answered NO to question 1, is the overall pain in the lower abdomen the same or worse than before your surgery?

A. Worse

B. Same

C. I don't know

2. Since your surgery, please choose one option that best describes the **pain in the lower abdomen**:

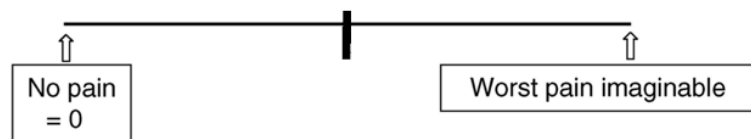
- A. Satisfied with my overall pelvic pain
- B. Minimally satisfied with my overall pelvic pain
- C. Undecided/same or I have worse overall pelvic pain
- D. I don't know

3. Since your surgery, did the **pain in the lower abdomen improve initially for some time and then come back**?

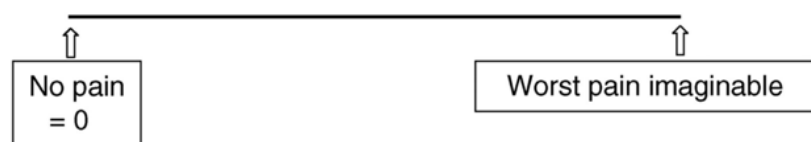
- A. YES
- B. NO
- C. I don't know

4. Please place a vertical mark on the line below to indicate the level of pain

Example: How would you rate your overall pain in scale below?



A. How would you rate your **overall pain in the lower abdomen** on the scale below since your surgery?



B. How would you rate your **pain in the lower abdomen during your periods** on the scale below since your surgery?

↑

No pain
= 0

↑

Worst pain imaginable

C. How would you rate your **pain in the lower abdomen between your periods** on the scale below since your surgery?

↑

No pain
= 0

↑

Worst pain imaginable

D. How would you rate your **pain during a bowel movement, especially during your periods**, on the scale below since your surgery?

↑

No pain
= 0

↑

Worst pain imaginable

E. How would you rate the **pain when you urinate, especially during your periods**, on the scale below since your surgery?

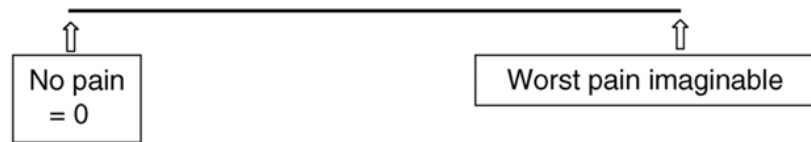
↑

No pain
= 0

↑

Worst pain imaginable

F. How would you rate your **pain with deep penetration during sex**, on the scale below since your surgery?



5. How many pregnancies have you had since your surgery? (please include miscarriages and abortions)

6. Are you **currently** pregnant?

A. YES

B. NO

7. How many times have you given birth since your surgery?

8. Are you currently taking birth control or a hormonal medication?

A. YES

B. NO

C. I don't know

IF you answered YES or I DON'T KNOW to question 6, please circle birth control/hormone medication you currently use:

A. Combination oral birth control

B. Progestin only pills

- C. Nuvaring
- D. Birth control patch
- E. Lupron (leuprolide) injection
- F. Depo Provera injection
- G. Orlissa pill
- H. Other: _____
- I. I don't know

9. Do you wish to get pregnant within the next year?

- A. YES
- B. NO
- C. I don't know

10. Have you been diagnosed with infertility since your surgery?

- A. YES
- B. NO
- C. I don't know

IF you answered NO or I DON'T KNOW to question 8, In the past or currently, have you had difficulty for at least a year in getting pregnant with a partner while actively trying?

- A. YES
- B. NO
- C. I don't know

11. Have you had any infertility treatments since your surgery?

A. YES

B. NO

IF you answered YES to question 9, what treatments have you received?

A. IVF

B. Clomid

C. Letrozole

D. Intrauterine insemination

E. Injectable hormones

F. Other: _____

G. I don't know

Please fill out questionnaire EHP-5 (see ATTACHMENT I)

Please fill out questionnaire Female sexual function index (see ATTACHMENT II)

APPENDIX III

Researcher Portion

Record number: _____

Patient name: _____

DOB: _____

G: ____ P: ____

Intraop findings:

Procedures performed: Circle all that apply

Laparoscopic endometriosis excision

Ovarian cystectomy

Cystoscopy

Ureterolysis

Appendectomy

Bladder nodule excision

Rectal shaving

Segmental bowel resection

Laparoscopic hysterectomy

Laparoscopic bilateral salpingo-oophorectomy

Laparoscopic unilateral salpingo-oophorectomy

Open Hysterectomy

Diaphragm surgery

Others: _____

Revised ASRM classification: _____

Circle all that apply:

1. Superficial endometriosis
2. Deep infiltrating endometriosis
3. Rectovaginal nodule
4. Obliterated cul-de-sac
5. Endometrioma
6. Bladder endometriosis
7. Endometriosis of the sigmoid or rectum
8. Ureteral endometriosis
9. Diaphragm
10. Endometriosis of Appendix
11. Hydrosalpinx
12. Other _____

Does the patient have intraoperative or preoperative imaging signs of adenomyosis? (please circle one choice below)

YES

NO

List all complications:

EHP-5 Score:

Female sexual function index Score: