Mirena® IUD's Effect on Fallopian Tube Fimbriae and Ovarian Cortical Inclusion Cyst Cell Proliferation

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites
Manhattan
Westchester
Basking Ridge
Commack
Monmouth
Rockville Center

Participating Institutions – If multicenter study coordinated by MSK:	**PI's Name**	**Site's Role**
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Combination-type oral contraceptives (COCs) have been shown to significantly reduce the risk of invasive epithelial ovarian cancer (IEOC); this protective effect may be achieved to a large extent through COCs ability to reduce cell proliferation in the fallopian tube fimbriae (FTF). The progestin-releasing Mirena® intra-uterine device (IUD) is an increasingly popular method of contraception, but it is not known if its use will reduce a woman"s risk of IEOC. Mirena® use does not block ovulation in most women, but it may release sufficient progestin to also reduce cell proliferation in the FTF. This study aims to evaluate the effects of the Mirena® IUD on cell proliferation in the FTF as a possible biomarker of protection against IEOC.

In this study, a Mirena® IUD will be inserted into volunteers scheduled for a risk-reducing salpingo-oophorectomy (RRSO) or risk-reducing salpingectomy (RRS) at Memorial Sloan Kettering Cancer Center (MSK). Alternatively, women with a Mirena® IUD already in place and who will be scheduled for an RRSO or RRS at MSK can also participate. We are seeking 14 evaluable participants. FTF tissue (and ovarian inclusion cyst tissue, when available) collected at the time of risk-reducing surgery will be tested by immunochemistry staining for Ki67 (a protein that is significantly increased when cells are preparing for division). The goal of this testing is to determine whether the cell proliferation in the FTF is reduced in these women compared to such proliferation during the normal cycle (data obtained under MSK IRB Protocol #14-165).

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- **Primary Objective**: To determine in women undergoing an RRSO or RRS at MSK whether cell proliferation in the FTF is reduced in those using a progestin-releasing Mirena® IUD compared to such proliferation during the normal menstrual cycle.
- **Secondary Objective**: To determine in women undergoing an RRSO at MSK whether cell proliferation in ovarian cortical inclusion cysts (CICs) is reduced in those using a progestin-releasing Mirena® IUD compared to such proliferation during the normal menstrual cycle.

3.0 BACKGROUND AND RATIONALE

Approximately 21,000 new diagnoses and 14,000 deaths occur each year as a result of invasive epithelial ovarian cancer (IEOC; also referred to as ovarian carcinoma or ovarian cancer) in the US.[1] Five-year survival is less than 50%, and there is currently no effective screening approach.[2] Preventive strategies are of paramount importance.

There are 5 main subtypes of ovarian cancer: high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous. All subtypes demonstrate a Mullerian-tissue phenotype except for mucinous tumors, which sometimes demonstrate a gastrointestinal phenotype.[3] High-grade serous ovarian cancer (HGSC) accounts for approximately 70% of ovarian cancer cases.[4] Until recently the favored proposed cell of origin of HGSC was the mesothelial ovarian surface epithelium (OSE).[5] The mechanism was entrapment of the OSE into OSE-CICs within the ovary with subsequent metaplastic transformation into Mullerian-type epithelium (Mullerian-CICs), which most commonly has the appearance of fallopian tube

epithelium. More recently, the Mullerian FTF has been proposed as the direct cell of origin of a high proportion of HGSCs;[6-12] this was based on the finding that the most common site of occult „ovarian cancer" lesions in BRCA1/2 mutation (BRCA1/2^{mut}) carriers undergoing an RRSO was the FTF. There is good evidence that many non-BRCA-associated HGSCs also develop in the FTF.[10] There is also good evidence that some ovarian cancers arise in Mullerian-CICs.[5,12,13]

COCs, with an estrogen and a progestin in each active pill, provide substantial protection against ovarian carcinoma.[14] The protective effect extends to all histological subtypes of ovarian cancer and lasts for more than 30 years after COC use is stopped.[14] The protective effect has also been found in BRCA1/2^{mut} carriers.[15-19] "Incessant ovulation" was long considered to be the driving force in ovarian cancer etiology,[20] and it was generally believed that the protective effect of COCs arose from their action of blocking ovulation. However, it is now clear that postmenopausal estrogen therapy (ET) significantly increases the risk of ovarian cancer and this effect is much reduced by the addition of a progestin.[21] Since postmenopausal ET use is not associated with any increase in ovulation, this suggests that endogenous and exogenous estrogen and progestin levels influence ovarian cancer risk directly.

Cell proliferation in the FTF over the menstrual cycle has been reported to closely follow cell proliferation in the endometrium.[22 23] There is proliferation throughout the follicular phase of the cycle, and little or no proliferation from a few days after ovulation with the rise in progesterone until the end of the cycle; our preliminary data confirm this (MSK IRB Protocol #14-165; PI K. Park, MD). To our knowledge, there are no data on cell proliferation in FTF or CICs from women using COCs or a Mirena® IUD. Furthermore, there is no literature on cell proliferation in CICs relative to the phase of the menstrual cycle.

We propose that the protection against HGSC from COC use is due in large part to the action of the progestin component of COCs as this component significantly reduces cell proliferation in the FTF and in CICs. A central role for proliferation in the etiology of many cancers was emphasized in two papers published in 1990,[24,25] and the supportive epidemiological evidence was presented by Preston-Martin and colleagues.[26] The recent paper by Tomasetti and Vogelstein[27] presented new evidence of the important association between proliferation and cancer rates. The clearest evidence of the importance in the etiology of a cancer site is the association between menopausal estrogen replacement therapy and endometrial cancer.[28-30] This association also provides the explanation of the strong association between obesity and endometrial cancer including its importance in premenopausal women through increasing the frequency of anovulation.[31,32] The effectiveness of an analysis based on cell proliferation to quantitatively explain the age incidence and many risk factors for the major female cancers can be found in references 33 and 34. A reduction in cell proliferation would be protective, as proliferating cell populations are more susceptible to carcinogenic effects due to increased chances of mutation and progression. (Note: the progestin component of COCs blocks cell proliferation in the endometrium and this is generally accepted as the mechanism of COC protection against endometrial cancer.)

We hypothesize that when a Mirena® IUD is used, despite its associated very low serum level of progestin (see below), cell proliferation in the FTF will be very low (comparable to the proliferation in the luteal phase of the menstrual cycle). We further hypothesize that the same may be true of cell proliferation within CICs. The results from this study will provide crucial information regarding the possible protection against IEOC from use of the Mirena® IUD.

FTF tissue from premenopausal women undergoing an RRSO or RRS and ovarian tissue from premenopausal women undergoing an RRSO will allow us to study the mechanism of protection against HGSC from COC use as well as the possible protection from use of the Mirena®. BRCA1/2^{mut} carriers are at high risk of ovarian cancer. They often choose to undergo RRSO surgery at a premenopausal age as this surgery is proven to dramatically decrease their ovarian cancer risk as well as their risk of breast cancer.[35] Tissue from these women is most appropriate for study as the protective effect of COCs against ovarian cancers is also seen in BRCA1/2^{mut} carriers.[15-19] Many other women with a strong family history of ovarian/breast cancer also choose to undergo an RRSO or RRS, and study of their FTF and their ovarian tissue, when available, is also appropriate.

We currently have an NCI-funded grant (1R21 CA181923-01A1; MSK IRB Protocol #14-165) to do a comprehensive study of proliferation in the FTF and CICs over the menstrual cycle and in the postmenopausal period using archived specimens from RRSOs conducted at MSK. Also, the University of Southern California and the British Columbia Cancer Agency (associated with the University of British Columbia), with which Dr. Pike is associated, also have an NCI-funded grant to study the effect of a COC on such proliferation. In this latter study, a COC is administered for 7-14 days before the RRSO procedure. Such short duration treatment should be sufficient to observe the effects on the FTF, as cellular proliferation in the FTF appears to be exquisitely sensitive to changes in the hormonal milieu.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a non-randomized study of the effect of Mirena® IUD use of at least 10 days before an RRSO or RRS on cell proliferation within the FTF and, when available, within ovarian CICs in women aged 35 through 50. The study will compare the results from 14 women using Mirena® with the results from 28 normally cycling women identified under MSK IRB Protocol #14-165 described above; all patients will be aged 35-50 years, and will have undergone the RRSO at MSK. To date, we have identified approximately 100 suitable controls and are continuing to identify further suitable controls among women who have recently undergone RRSOs at MSK. The balancing/matching factors will be BRCA status (BRCA1/BRCA2/BRCA-ve), age (35-39/40-44/45-50), parity (nulliparous/parous), and BMI (<30/30+ kg/m^2). As each Mirena® patient completes the study and is deemed evaluable, she will be matched on each of these factors with 2 controls. If only one exact match is available, then her second control will be chosen according to the balancing scheme of Pocock and Simon,[36] with choice between controls with equal (low) imbalance being made with preference for balancing in the following order: BRCA, age, parity, and BMI. If no exact match is available, the same scheme will be used to choose the 2 controls. This approach

will ensure that at the completion of the study with 14 Mirena® patients and 28 controls, the matching criteria will be closely balanced between the 2 groups. If at any stage of the choice of controls, more than one equally good control is identified, the one with the most recent RRSO will be chosen.

We expect to enroll women during months 3-30 of the study. Immunohistochemical analysis of the tissue will be done throughout and completed in months 31-33. Data analysis and a manuscript describing the results will be completed in months 34-36.

4.2 Intervention

This current proposal is intended to study the effect of use of the increasingly popular progestin-containing (levonorgestrel, or LNG) Mirena® IUD on FTF and CIC proliferation. The Mirena® IUD releases 20 mcg of LNG per day and is associated with a very low serum concentration of LNG, no more than 10% of the average LNG concentration with a standard LNG-containing COC.[37-419] We propose that the Mirena® IUD be in use for $\geq$10 days before the RRSO or RRS.

Use of an earlier version of a Mirena®-type IUD releasing 30 mcg/day of LNG was found in a single study to be associated with a concentration of LNG in the fallopian tube equal to that seen in women using a standard 250 mcg LNG COC;[42] the dose of LNG in the most commonly used current COC is 150 mcg. Significant improvement of symptoms of endometriosis are commonly seen with treatment with a Mirena® IUD.[43] These results suggest that the daily dose of progestin released by the IUD may be sufficient to affect the fallopian tube.

FTF cell proliferation is observed within a few days of the start of the follicular phase of the menstrual cycle (estrogen exposure with very low progesterone), with little or no proliferation from a few days after ovulation until the end of the cycle. We estimate that cell proliferation will be maximal from early on after the start of menses, and certainly by day 5 until around day 15 of the cycle. This study is to determine whether FTF cell proliferation during this period is significantly reduced if the woman is using a Mirena® IUD. We have therefore chosen the follicular phase (approximately between 5 and 15 days after the start of the cycle and to be determined by blood sample on the day of surgery) as the appropriate period in which to compare cell proliferation between the Mirena® group and the retrospective control group. For the Mirena® group, it is essential that the participant has very low serum progesterone (P4) at the time of sampling; if her P4 is high at the time of sampling, it will not be possible to determine whether or not any observed low proliferation rate is due to the endogenous P4 level. We will measure estradiol (E2) and P4 from a blood sample taken on the day of surgery. A P4 value >1 ng/ml will be considered unsatisfactorily high; if such a value is found, the sample FTF and CIC cell proliferation values will be ignored and the patient will not be counted towards the 14 Mirena®-treated patients planned for the study. The E2 measurement will be performed to confirm that there is follicular phase estradiol production: if E2 is <30 pg/ml, the samples will be ignored and the patient will not be counted towards the planned 14 evaluable subjects. This E2 restriction is necessary as Mirena® use is generally associated with regular premenopausal estrogen levels.

If the hypothesized effects are seen, Mirena® use may be an attractive contraceptive option for BRCA1/2^{mut} carriers and other women at high risk of IEOC.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

This study is investigating the effects of the Mirena® IUD. This is an FDA approved intrauterine contraceptive that is indicated for use up to 5 years. It is also indicated for the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception. Mirena® contains 52 mg of levonorgestrel (LNG), which is released at a rate of approximately 20 mcg/day.

Mirena® will be supplied for this study at no cost by its manufacturer, Bayer HealthCare Pharmaceuticals.

Mirena® is available in a carton of one sterile unit (NDC# 50419-423-01). Mirena® is supplied sterile. Mirena® is sterilized with ethylene oxide and should not be resterilized. It is for single use only. It should not be used if the inner package is damaged or open. It should be inserted before the end of the month shown on the label. It should be stored at 25°C (77°F), with excursions permitted between 15–30°C (59–86°F).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

We will recruit women seeking an RRSO or RRS at MSK, including BRCA1/2^{mut} carriers and women with a strong family history of breast and/or ovarian cancer.

Approximately 130 women undergo an RRSO or RRS per year at MSK, of whom ~30% meet our eligibility criteria. Enrollment will be carried out over 30 months. We expect there will be ~97 eligible women receiving an RRSO or RRS during this recruitment period.

6.1 Subject Inclusion Criteria

- Women between 35 and 50 years of age (inclusive)
- Women who will be scheduled to undergo an RRSO or RRS
- Women who will have at least one fallopian tube removed for risk-reducing reasons (with or without removal of ovar(ies))
- Women who are willing to have a Mirena® IUD inserted at least 10 days prior to risk-reducing surgery or who already have the Mirena® in place
- Women using non-hormonal forms of contraception
  (*Note*: If a copper IUD is being used, the IUD must be removed prior to or at time of Mirena insertion.)

6.2 Subject Exclusion Criteria

- Any medical contraindication to use of a Mirena® IUD, including:
  - Pregnancy (a pregnancy test is required prior to study entry)
  - Known uterine anomaly that distorts the shape of the uterine cavity
  - Acute pelvic inflammatory disease
  - Postpartum endometritis or endometrial infection
  - Known or suspected uterine or cervical neoplasia
  - Known history or suspected breast cancer or other progestin-sensitive cancer

  - Uterine bleeding of unknown etiology.
  - Untreated acute cervicitis, vaginitis, or other lower genital tract infections
  - Acute liver disease or liver tumor (benign or malignant)
- Use of tamoxifen, raloxifene, or chemotherapy within the previous 6 months
- Positive pregnancy test
- Breastfeeding
- Use of a copper IUD if the patient is not willing to have it removed prior to surgery and replaced with a Mirena® IUD

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient"s treatment team, the protocol investigator, or research team at Memorial Sloan Kettering Cancer Center (MSK). If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. Patients identified in this manner would subsequently be approached for study enrollment after consultation with their treating physician.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary for the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSK in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Potential study participants who meet our basic inclusion/exclusion criteria will be approached by their physician to volunteer for this study. If the patient indicates a willingness to participate, an investigator will explain the study in detail. Women who volunteer and sign an informed consent will have a Mirena® IUD inserted by a trained physician if they do not already have the Mirena® IUD in place. Our goal is to obtain 14 evaluable patients. We anticipate needing to consent 28 women in order to obtain the 14 evaluable patients because some patients may not be in the follicular phase at the time of their RRSO/RRS, which is necessary for appropriate evaluation of cell proliferation.

8.0 PRETREATMENT EVALUATION

Women who consent to the study will have up to two in-person study visits prior to RRSO/RRS (see below) occuring in conjunction with their regular care visits.

Patients determined likely to be eligible will be approached about the study at their first regular care visit with their surgeon if possible. Any patient without a Mirena® already in place and interested in participating should be scheduled to have the Mirena® placed on study at a regular care visit at least 10 days prior to surgery.

9.0 TREATMENT/INTERVENTION PLAN

Following informed consent to the study and at any time prior to surgery, all patients will complete a short questionnaire. This is a simple structured form based on forms in use in epidemiological studies at MSK. It will be used to request a brief reproductive history and to capture inclusion and exclusion criteria information.

All patients will have a serum pregnancy test at the time of a clinical blood draw or a urine pregnancy test. For patients planning to have a Mirena® placed on study, this test must be done prior to Mirena® placement. If this test is positive, the patient is ineligible for the study and the Mirena® will not be placed.

Patients who will have a Mirena® placed on study will undergo chlamydia and gonorrhea testing at the time of Mirena® placement. If patients are positive for chlamydia or gonorrhea, they will be treated. The Mirena® will be inserted according to the technique described in the prescribing information.

Patients can have the Mirena® placed at a regional site by an investigator, provided that Investigational Drug Services and the regional pharmacy are given at least 3 business days" notice.

Day of Surgery: On the day of surgery, we will collect a blood sample in a 10mL red top tube with no additives for measurement of E2, P4, and LNG. All patients who had the Mirena® placed on study will have it removed at the time of RRSO/RRS. FTF processing and, if applicable, CIC processing will occur as described below.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Ovarian tissue (if removed) and fallopian tube(s) will be submitted *in toto* as per standard MSK clinical protocol for RRSO/RRS specimens. According to this protocol, the fimbriated end of the fallopian tube is amputated and serially sectioned along its length, and submitted *in toto*. This maximizes the amount of fallopian tube epithelium available for histological examination. This is part of normal clinical care and is not affected by this study.

Blood will be collected in 10mL red top tubes according to standard procedures and processed by Dr. Irene Orlow"s Molecular Epidemiology Laboratory at Memorial Sloan Kettering Cancer Center. This laboratory is located on the 7th floor of the Schwartz building, and the research blood tube will be delivered in accordance with instructions on the requisition uploaded to Study Related Documents (specifically to Other Specimen Related Documents) in the Protocol Information Management System (PIMS).

Serum will be sent to the University of Southern California Reproductive Endocrine Research Laboratory at the address below, and E2, P4, and LNG will be assayed under the direction of Dr. Frank Stanczyk (fstanczyk@att.net) for comparability to the assays being conducted in the COC study:

USC Reproductive Endocrine Research Laboratory
1321 North Mission Road
Livingston Research Building, Room 207
Los Angeles, CA 90033
Attn: Stan Patel
Phone: 323-224-5590 (office)
310-462-1259 (cell)
sherfaraz.patel@med.usc.edu (email)

Specimens to be shipped for testing at the USC Reproductive Endocrine Research Laboratory will be labeled with their sample IDs. A shipping manifest will accompany the shipment and will provide the following information: Processing and shipping lab at MSKCC, list of sample IDs, date of collection, type of specimen, and sample volume. No other participant identifiers will be sent to USC, within the shipment or via email. Specimens will be shipped overnight on dry ice. Shipments will be agreed on in advance and in general will occur on Monday, Tuesday, or Wednesday, avoiding vespers of holidays and weekends.

Cell Proliferation Measurements

We will only use specimens of FTF and ovaries after standard pathology review has determined that there is no evidence of malignancy or a premalignant lesion in the specimens.

10.1 FTF Cell Proliferation

Fixation and tissue processing will be conducted according to standard MSK Pathology Department procedures. To assess proliferation in the FTF epithelium, a „random" block containing fimbriae will be obtained for each patient and adjacent 1 μm sections cut,

deparaffinized, and hydrated. FTF cells are extremely tightly packed and 1 μm sections have been found necessary for successful automated counting of individual cells. All slides will be subject to antigen retrieval for IHC analysis. The slides will be stained for Ki67(MIB-1; cell proliferation), PAX-8 (secretory cells),[44-45] and estrogen receptor α (ERα), and progesterone receptor A/B (PR) using MSK standard methods with MIB-1 (Dako Cytomation, Carpenteria, CA, USA), PAX-8 (AC1438A, Biocare, Concord, CA), ERα (Clone SP1, Ventana Medical systems, Hoffmann-La Roche, Nutley, NJ) and PR (Clone 1E2, Ventana Medical systems, Hoffmann-La Roche, Nutley, NJ). The slides will then be scanned using the Aperio® slide scanning system and quantitative analysis of the labeling (% positive cells) will be done with a systematic „blind" choice of regions of interest (ROIs) using an overlaying grid covering the whole slide until at least 1,000 FTF epithelial cells have been counted. The count of total cells and positive cells is done by a validated automated system. We will use manual mapping of the adjacent PAX-8 stained slides to estimate the proportion of FTF cells that are ciliated for each ROI and thereby estimate the proliferation index for secretory and ciliated cells separately. The proportion of FTF cells that are secretory in the follicular phase of the cycle is estimated to be ~45%.[23,45] Additional slides from other random blocks will be obtained if the slide does not contain sufficient FTF epithelial cells. This will be carried out under the supervision of the MSK study pathologist, Dr. Kay Park.

The main focus of analysis will be all FTF epithelial cells. Separate analyses of secretory and ciliated cells will be performed in order to gain potentially useful information. The main analysis will be conducted with staining for Ki67; the other stains may be of help in understanding the Ki67 results.

10.2 Cell Proliferation in the CICs

Fixation and tissue processing will again be done according to standard MSK Pathology Department procedures. To assess proliferation in the CIC epithelium, all hematoxylin and eosin (H&E) stained slides will be inspected to find the block with the largest number of CICs. This block will have adjacent 3 μm sections cut, deparaffinized, and hydrated (3 μm sections are the thinnest sections that can be successfully cut from an ovary). All slides will be subject to antigen retrieval for IHC analysis. The slides will be stained for Ki67, PAX-8, ERα, and PR using methods as described above. The slides will also be stained for calretinin to detect OSE cells (5A5, NCL-L-Calretinin, Leica Microsystems, Buffalo Grove, IL). The slides will then be scanned using the Aperio® slide scanning system and quantitative analysis of the labeling (% positive cells) will be done for all CICs. The count of total cells and positive cells is done by a validated automated system. We will use manual mapping of the adjacent PAX-8 stained slides to estimate the proportion of FTF-type cells that are secretory for each Mullerian CIC, and thereby estimate the proliferation index for secretory cells separately. Additional slides from other blocks will be obtained if the slide does not contain sufficient FTF-like epithelial cells. Previous studies suggest that ~60% of the slides will contain no CICs, and the average number of CICs on slides with ≥1 CIC will be ~10 [44,46]. A detailed study by Li *et al*.[37] found that 66% of CICs are PAX-8 positive (FTF secretory-like), 12% are tubulin positive (FTF ciliated-like), and 22% are calretinin positive (OSE-like), and that the average number of cells per CIC was 146 (no breakdown by type of CIC was given). We therefore estimate that the number of PAX-8 or tubulin positive cells per CIC-containing slide will be ~1,135 (~960 and ~175 for PAX-8 positive and tubulin positive, respectively), while

the number of calretinin positive cells will be ~320. We plan on analyzing multiple slides, sufficiently separated from each other to avoid overlap of cells, until we have 1,000 PAX-8 positive cells in total; this will give us in total ~2,115 PAX-8 positive cells, ~385 tubulin positive cells, and ~705 calretinin positive cells. This will be carried out under the supervision of the MSK study pathologist, Dr. Kay Park.

The main focus of analysis will be the FTF-like cells combined (in agreement with the analysis of FTF cell proliferation in the FTF described above) and of calretinin positive cells. Separate analysis of PAX-8 positive cells will be conducted to gain potentially useful information.

11.0 TOXICITIES/SIDE EFFECTS

Insertion of the Mirena® IUD is an office procedure. A speculum examination is performed, and the cervix is grasped with a tenaculum. The Mirena® IUD system is advanced into the uterine cavity, where the Mirena® is deployed. During insertion of the Mirena® IUD, reported side effects include pain, uterine cramping, dizziness, and lightheadedness. Uncommonly, bleeding occurs at the tenaculum site and requires use of hemostatic measures. There is a remote chance of uterine perforation during placement of the Mirena® (approximately 1/1000); this can cause injury to surrounding organs or tissues as well as extra-uterine placement of the IUD. Expulsion of the IUD occurs less than 5% of the time. Other uncommon side effects that have been reported with Mirena® IUD use include amenorrhea, dysmenorrhea, benign ovarian cysts with associated complications, headache, acne, depression, vaginal discharge, nausea, back pain, unusual hair growth or alopecia, vulvovaginitis, breast tenderness/ pain, and pelvic inflammatory disease or endometritis.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary outcome is the extent of proliferation in the FTF in women on the Mirena® IUD compared to FTF proliferation during the normal follicular phase. Women will be deemed evaluable for this primary outcome if they successfully underwent placement of the Mirena® IUD, received a RRSO/RRS as planned, and had a P4 value ≤1 ng/ml.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (e.g., a change in diagnosis), the patient will be removed from the study.

Mirena® insertion on study will be immediately stopped at any time the subject requests, and she will be removed from the study. Similarly, if at any time after the insertion on study but before the RRSO/RRS, the subject requests that the Mirena® be removed, the Mirena® will be removed and the subject will be taken off the study. Additionally, should expulsion of the Mirena® occur prior to surgery or should it be discovered that the Mirena® was placed in an extra-uterine location, the patient will be removed from the study.

14.0 BIOSTATISTICS

Our study is powered based on obtaining evaluable data from 14 women.

Our primary endpoint is the difference in cell proliferation in the FTF epithelium (FTFE) of women on a Mirena® and control women during the follicular phase of their menstrual cycle (14 women in the Mirena® group vs 28 women in the control group). Experience in analyzing data on cell proliferation in the FTFE of different women shows that cell proliferation results should be logarithmically transformed to achieve a more normal distribution of values. We will use analysis of variance for this analysis. All analyses will be done using Stata 12 (Stata Corporation, College Station, TX, USA).

In their study of proliferation in normal premenopausal women in the follicular phase of the menstrual cycle, Donnez et al.[22] found a standard deviation on a logarithmic scale of 1.17. This is very similar to the results from our pilot study where we analyzed proliferation in the FTFE of 5 such premenopausal RRSO patients in the follicular phase and found a standard deviation of 1.21. (This standard deviation is greatly in excess of the standard deviation predicted by assuming that all women have the same true proliferation rate and shows that our analysis of a total 2,500 cells per woman is more than sufficient to ensure that this number has only a minor effect on the between women standard deviation.) The difference in cell proliferation observed by Donnez et al.[22] between the follicular phase and the luteal phase of the cycle was ~88% (a 75% reduction in the „early secretory" phase and a 100% reduction in the „late secretory" phase). These results were confirmed in our pilot study, in which we analyzed specimens from 5 women in the follicular phase and 5 women in the luteal phase of the cycle at their RRSO.

Using the slightly larger value of 1.21 as an estimated standard deviation between different women, our sample size of 14 Mirena® women vs 28 control women affords us 90% power to detect a 72% decrease, and an 80% power to detect a 67% decrease, in FTFE proliferation with a two-sided alpha level of 5%. This shows that we have adequate power to detect a difference between the Mirena® group and the control group if the Mirena® affects the FTFE to the same extent as is achieved in the luteal phase of the cycle.

We have no preliminary data on cell proliferation in CICs in premenopausal women, and there are no data in the literature as far as we have been able to discern.. There are certainly no data on cell proliferation in CICs by phase of the menstrual cycle. This aspect of the proposal must therefore be considered exploratory. In the study by Li et al.,[45] where no results are given by menopausal status, cell proliferation in PAX-8 positive CICs was reported as 1.1%, some 10 times higher than in calretinin positive cells. This suggests that we may have sufficient power to investigate FTF-like cells in CICs, but not sufficient power to investigate calretinin positive cells.

15.0 RESEARCH PARTICIPANT REGISTRATION/ RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Eligibility will be confirmed for all patients as defined in the section entitled "Criteria for Patient/Subject Eligibility". The screening eligibility checklist will be completed at time of consent to the study. Informed consent will be obtained following the procedures outlined in the section entitled "Informed Consent Procedures".

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist, and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

This is not a randomized study and no randomization of treatment will occur. Comparison to non-study participants will be on a 2:1 matched basis as outlined in the Study Design Section.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

All efforts will be made to ensure maintenance of patient confidentiality and HIPAA compliance. All data will be maintained on the MSK Clinical Research Database and the Protocol Management System. All data collected will be stored on a secure server at MSK and access will be password protected. This will only be accessible by trained study investigators.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year and more frequently if indicated.

Research Staff will verify eligibility, informed consent, and accuracy of the demographic data collected for all patients whenever a patient is enrolled onto the study. This will ensure the quality of the data collected and verify the presence of all pertinent study data and documents.

16.2 Data and Safety Monitoring

The study investigators will be responsible for ensuring the safety of the study participants. The investigators will stress the importance of reporting adverse events to the participants and the investigators will assess for adverse events at each instance of contact with the participants. Should adverse events occur, the study investigators will document these appropriately in the medical record and report these events to the IRB. CTCAE Version 4.0 will be used to assess adverse events.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://mskweb5.MSK.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs: the *Data and Safety Monitoring Committee* (DSMC) for Phase I and Phase II clinical trials, and the *Data and Safety Monitoring Board* (DSMB) for Phase III clinical trials. These committees report to the Center"s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

17.1 PROTECTION OF HUMAN SUBJECTS

Every effort will be made to ensure the safety of our patients and the confidentiality of their medical information. During the enrollment and consent process, all risks, benefits, side effects, and alternatives will be discussed. Also, it will be stressed that this is a voluntary study and that the patient can withdraw without prejudice at any time.

Benefits and Risks: The potential benefit of this study is to understand the way in which progestin, as delivered by a Mirena® IUD, affects tubal cell proliferation. As tubal proliferation appears to be related to the genesis of epithelial ovarian cancer, the provision of this information could have impact on the use of Mirena® IUD as a preventative measure for ovarian carcinoma. While this information could have a potentially vast benefit to society, there will be no direct benefit to the patients in the study as they will all be undergoing RRSO/RRS *a priori*.

The risks of participation include the risks associated with Mirena® IUD insertion and use, as outlined in the Toxicities and Side Effects Section (11.0). Given the rarity of those side effects and the very short use of the Mirena® IUD in these patients, it is unlikely that participants will incur injury as a result of participation.

Alternatives: The current standard treatment option for patients eligible for this study would be surgery without the insertion of the Mirena® IUD. A patient"s decision on whether or not to participate in this study will not affect the availability of standard, supportive, or other investigational treatment at MSK.

Costs: There will be no additional cost incurred by the patients who participate in the study. The Mirena® IUD systems will be provided at no charge by the manufacturing company, Bayer. Patients will not be charged for IUD insertion or removal, nor will they be charged for chlamydia or gonorrhea testing or associated tests.

Voluntary Nature of the Study: Participation in this study is entirely voluntary.

Inclusion of Children in Research: This protocol/project does not include children because the number of children undergoing RRSO/RRS is limited. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Patients will be informed of the extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments). The study will seek in every way to protect the rights of human subjects. No patient will be required to participate in the study, and participation or lack of participation will not affect the patient"s subsequent care or treatment.

The patient will not incur any financial cost as a result of participation in the study. Participation will be entirely voluntary and subjects will not be reimbursed for participation in the study. Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular

patient in the study. All adverse events will be fully disclosed to the IRB in a timely fashion as required.

17.1 Privacy

MSKCC"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30 days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows.

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number

- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject"s condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI"s signature and the date it was signed are required on the completed report.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.1 REFERENCES

1. Siegel R, et al. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65: 5-29.
2. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305:2295-303.
3. Gilks CB. Molecular abnormalities in ovarian cancer subtypes other than high-grade serous carcinoma. J Oncol 2010;2010:740968.
4. Kobel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol 2010;29:203-11.
5. Auersperg N, Wong AS, Choi KC, et al. Ovarian surface epithelium: biology, endocrinology, and pathology. Endocr Rev 2001;22:255-88.
6. Piek JM, Verheijen RH, Kenemans P, et al. BRCA1/2-related ovarian cancers are of tubal origin: a hypothesis. Gynecol Oncol 2003;90:491.
7. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. Am J Obstet Gynecol 2004;191:718-32.
8. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol 2006;30:230-6.
9. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol 2007;19:3-9.
10. Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. J Clin Oncol 2008;26:5284-93.
11. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31:161-9.
12. Kurman RJ, Shih I. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2010;34:433-43.
13. Pothuri B, Leitao MM, Levine DA, et al. Genetic analysis of the early natural history of epithelial ovarian carcinoma. PLoS ONE 2010;5:e10358.
14. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303-14.
15. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Eng J Med 1998;339:424-8.
16. McGuire V, Felberg A, Mills M, et al. Relation of contraceptive and reproductive history to ovarian cancer risk in carriers and noncarriers of BRCA1 gene mutations. Am J Epidemiol 2004;160:613-8.
17. Whittemore AS, Balise RR, Pharoah PD, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer 2004;91:1911-5.
18. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 2007;8:26-34.
19. Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev 2009;18:601-10.
20. Fathalla MF. Factors in the causation and incidence of ovarian cancer. Obstet Gynecol Surv 1972;27:751-68.
21. Pearce CL, Chung K, Pike MC, Wu AH. Increased ovarian cancer risk associated with menopausal estrogen therapy is reduced by adding a progestin. Cancer 2009;115:531-9.
22. Donnez J, Casanas-Roux F, Caprasse J, et al. Cyclic changes in ciliation, cell height, and al. Fertil Steril 1985;43:554-9.
23. George SH, Milea A, Shaw PA. Proliferation in the normal FTE is a hallmark of the follicular phase, not BRCA mutation status. Clin Cancer Res 2012;18:6199-207.

24. Ames BN, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. Science 1990;249:970-1.
25. Cohen SM, Ellwein LB. Cell proliferation in carcinogenesis. Science 1990;249:1007-11.
26. Preston-Martin S, Pike MC, Ross RK, et al. Increased cell division as a cause of human cancer. Cancer Res 1990;50:7415-21.
27. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science 2015;347:78-81.
28. Smith DC, Prentice R, Thompson DJ, et al. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293:1164-7.
29. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293:1167-70.
30. Mack TM, Pike MC, Henderson BE, et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976; 294:1262-7.
31. Siiteri PK. Steroid hormones and endometrial cancer. Cancer Res 1978;38:4360-6. Review.
32. Henderson BE, Casagrande JT, Pike MC, et al. The epidemiology of endometrial cancer in young women. Br J Cancer 1983;47:749-56.
33. Pike MC, Krailo MD, Henderson BE, et al. „Hormonal" risk factors, „breast tissue age" and the age-incidence of breast cancer. Nature 1983;303:767-70.
34. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. Oncogene 2004;23:6379-91.
35. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80-7.
36. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31:103-5.
37. Lockhart FB, Emembolu JE, Konje JC. Serum and peritoneal fluid levels of levonorgestrel in women with endometriosis who were treated with an intrauterine contraceptive device containing levonorgestrel. Fertil Steril 2005;83:398-404.
38. Hidalgo MM, Hidalgo-Regina C, Bahamondes MV, et al. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel–releasing intrauterine system. Contraception 2009;80:84-9.
39. Seeber B, Ziehr SC, Gschlieber A, et al. Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system. Contraception 2012;86:345-9.
40. Edelman AB, Carlson NE, Cherala G, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. Contraception 2009;80:119-27.
41. Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics of a combined oral contraceptive in obese and normal-weight women. Contraception 2010;81:474-80.
42. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. Clin Endocrinol 1982;17:529-36.
43. Lockhart FB, Emembolu JO, Konje JC. The evaluation of the effectiveness of an intrauterine-administered progestogen (levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease. Hum Reprod 2004;19:179-84.
44. Bowen NJ, Logani S, Dickerson EB, et al. Emerging roles for PAX8 in ovarian cancer and endosalpingeal development. Gynecol Oncol 2007;104:331-7.
45. Li J, Abushahin N, Pang S, et al. Tubal original of „ovarian" low-grade serous carcinoma. Modern Pathol 2011;24:1488-99.

20.1 APPENDICES

A. Mirena® Prescribing Information