Ob/Gyn & Women’s Health Perspectives

An Update for Physicians from Cleveland Clinic’s Ob/Gyn & Women’s Health Institute

IN THIS ISSUE

Battling Weight Gain Together in Cyberspace
Update on the Role of PARP Inhibitors in Epithelial Ovarian Cancer
Investigation of Versican Proteolysis in Leiomyoma Sheds Light on Pathogenesis

Laparoscopic vs. Robotic Surgery for Endometriosis: How Do Outcomes Compare?
Dear Colleagues and Friends:

One of the most interesting aspects of an obstetrics and gynecology practice is the array of medical issues we address on a daily basis. This issue of Ob/Gyn & Women’s Health Perspectives reflects this, with topics ranging from fibroid research to an innovative weight management program to PARP inhibitors for advanced ovarian cancer. The topics demonstrate our institutional focus on advancing research, clinical practice and services, and on providing the best possible care for patients.

Cleveland Clinic is proud to be recognized as a national leader in gynecology in U.S. News & World Report’s “2017-18 Best Hospitals” rankings. We appreciate your referrals and entrusting the care of your patients to us. I welcome — in fact, encourage — your feedback, questions and comments.

Best,

Tommaso Falcone, MD, FRCSC, FACOG
Professor & Chairman, Department of Obstetrics and Gynecology
Chairman, Ob/Gyn & Women’s Health Institute
216.444.1758  |  falcont@ccf.org

Managing Editor: Sandra Erlanger
Art Director: Amy Buskey-Wood
Cover Photo: Tom Merce
Marketing: Samantha Brainard, Nicole Ward, Suzanne Anthony, Kristin Swenson

Ob/Gyn & Women’s Health Perspectives is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

© 2017 The Cleveland Clinic Foundation

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,500 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 18 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2017, Cleveland Clinic ranked No. 2 in U.S. News & World Report’s “Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 23rd consecutive year) and urologic care.
Laparoscopic vs. Robotic Surgery for Endometriosis

Outcomes can be equally good with either procedure

Contrary to the common expectation that robotic assistance can improve the outcomes of endometriosis surgery, a study found no evidence it is either superior or inferior to traditional laparoscopic technique.

“Both robotic and laparoscopic surgery improve quality of life and relieve pain when the procedures are done by experts in endometriosis,” says Tommaso Falcone, MD, Chairman, Ob/Gyn & Women’s Health Institute at Cleveland Clinic.

This conclusion is the result of a multicenter, randomized clinical trial comparing the use of traditional laparoscopic surgery with robot-assisted surgery in women with endometriosis. The primary outcome was operative time. Secondary outcomes included perioperative complications and quality of life.

No difference in operative time was seen between the two groups. Nor were there differences in blood loss, intraoperative complications, postoperative complications, rates of conversion to laparotomy or quality-of-life improvement.

Details of the study were published in the April 2017 issue of Fertility & Sterility.¹

Surgeon’s experience trumps technology

The equality of the two operative techniques did not surprise Dr. Falcone. An experienced endometriosis surgeon, he has co-edited multiple textbooks on robotic and laparoscopic techniques. He feels the surgical approach does not matter as much as how well the disease is understood.

“Due to the complex nature of pain in endometriosis, knowledge of the disease process and what the disease looks like in a patient, plus familiarity with the anatomy, are more important to outcomes than the surgical technique or technology used,” he says.

He admits that robotic surgery has a certain cachet. However, he emphasizes that the technology itself does not improve outcomes.

“If you are a good driver, it’s unlikely that a more expensive car like a Ferrari will make you drive better. It’s the same with surgery,” he says. “The robot isn’t magical.”

Both are excellent options

Gynecologists know endometriosis as a chronic, inflammatory, estrogen-dependent disease associated with significant quality-of-life challenges, including pain and infertility. Endometriosis also poses a substantial economic impact in terms of decreased productivity and healthcare costs.

Although endometriosis has a high recurrence rate after surgical treatment, the study found surgery was largely successful in relieving pain and restoring quality of life, regardless of the approach used.

Patients in both groups reported significant but equal improvement on condition-specific quality-of-life outcomes at six weeks and six months, as measured by the Short Form 12 Health Survey and Endometriosis Health Profile-30 Questionnaire.

“We want to reinforce that surgery for endometriosis works,” says Dr. Falcone. “However, the pain associated with

Who might benefit from robotic surgery?
In the era of cost savings, it may be difficult to justify the additional cost of a robotic procedure for the average endometriosis patient, Dr. Falcone notes. Nevertheless, there are times when robotic technique could be helpful.

“In complex endometriosis cases requiring ureter and bowel resections, the robot could be an advantage,” he explains. “However, in this study we didn’t test it to see if it might add value.”

Nor did the study evaluate whether a robot could increase the level of care provided by those surgeons who are less experienced with conventional laparoscopic surgery.

“Our study was not designed to evaluate this. But if an endometriosis surgeon is already skilled in laparoscopic technique, the robot will make no difference,” Dr. Falcone concludes.

Dr. Falcone may be reached at 216.444.1758 or falcont@ccf.org.

Despite better cytoreductive surgery and dose-dense and intraperitoneal chemotherapy regimens that have improved overall outcomes for ovarian cancer patients, epithelial ovarian cancer remains the most lethal gynecologic cancer in the United States. Most ovarian cancers are diagnosed at an advanced stage because we lack effective screening.

The role of PARP and PARP inhibitors
Poly (ADP-ribose) polymerase (PARP) is a family of proteins involved in repairing single-strand DNA breaks. PARP1 accounts for more than 90 percent of cellular DNA repair activity.

A class of drugs known as PARP inhibitors has been used as maintenance therapy after response to platinum-based regimens or monotherapy for recurrent ovarian cancer patients since 2014, when they were approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These drugs — olaparib, niraparib, rucaparib, veliparib and talazoparib — are generally well-tolerated, with the most common side effects being anemia, fatigue, nausea/vomiting and diarrhea. Thrombocytopenia is more common with niraparib.

Fifteen to 24 percent of ovarian cancer patients have a hereditary form of the disease that affects the homologous recombination (HR) pathway, the most reliable and important of six DNA repair pathways. The tumor suppressor genes...
BRCA1 and BRCA2 account for approximately 75 percent of these germline alterations. Somatic BRCA1/2 mutations have been reported in 6 percent of cases. Because ovarian cancer patients with BRCA mutations are HR pathway deficient, they are more sensitive to PARP inhibitors.

**PARP inhibitors: current research**

**Olaparib** is the first PARP inhibitor studied extensively and FDA approved for treatment of patients with recurrent ovarian cancer with germline BRCA mutations who received three or more prior lines of chemotherapy.

A recent phase II clinical trial investigating maintenance olaparib vs. placebo in recurrent platinum-sensitive ovarian cancer after response to platinum-based chemotherapy showed significant improvement in progression-free survival (PFS) in the olaparib arm compared with the placebo arm. PFS and overall survival benefits were more prominent in patients with a germline BRCA mutation.

The EMA has also approved olaparib as maintenance treatment for patients with relapsed BRCA-mutated, high-grade serous ovarian cancer who have responded to platinum-based chemotherapy. Olaparib is now the subject of two phase III trials (SOLO I and II).

**Niraparib** is a selective PARP1 and PARP2 inhibitor recently FDA approved for patients with recurrent ovarian cancer with germline or somatic BRCA mutation after two or more lines of prior chemotherapy. The ARIEL II and III trials are phase II and III trials investigating the role of rucaparib in recurrent ovarian cancer.

**Genomic tests to predict response to PARP inhibitors**

Two genomic tests have been developed to predict response to PARP inhibitors among patients without germline or somatic BRCA mutations. One measures genomic instability based on three independent tests of tumor tissue. A high score was shown to predict response to niraparib in the phase III NOVA trial.

A second test combines the status of somatic BRCA mutations and the percentage of genomewide loss of heterozygocity to define three subgroups that correlate with response to rucaparib in the ARIEL II trial.

**Clinical trials at Cleveland Clinic**

Cleveland Clinic’s Ob/Gyn & Women’s Health Institute is participating in several phase III clinical trials of PARP inhibitors. One is investigating veliparib as chemotherapy and maintenance therapy (GOG-3005). Another is examining niraparib as maintenance therapy (GOG-3012) in patients with newly diagnosed, advanced-stage ovarian cancer undergoing primary therapy.

Several other trials are investigating the role of olaparib alone or in combination with the oral antiangiogenic drug cediranib, compared with traditional chemotherapy in patients with recurrent platinum-sensitive (NRG-GY004) and platinum-resistant (NRG-GY005) ovarian cancers.

The data are promising regarding PARP inhibitors, especially in recurrent ovarian cancer, and we are awaiting results of current trials in patients with newly diagnosed ovarian cancer as part of primary therapy.

**ABOUT THE AUTHOR**

Dr. Mahdi is a gynecologic oncologist in the Ob/Gyn & Women’s Health Institute at Cleveland Clinic. He can be reached at 216.445.7069 or mahdih@ccf.org.
Investigation of Versican Proteolysis in Leiomyoma Sheds Light on Pathogenesis

By Ndye-Aicha Gueye, MD; Timothy J. Mead, PhD; Christopher D. Koch; Charles V. Biscotti, MD; Tommaso Falcone, MD; and Suneel S. Apte, MBBS, D Phil

How versican impacts extracellular matrix-dependent growth in uterine fibroids

Leiomyoma is the most common pelvic tumor occurring in women, affecting 70 to 80 percent of premenopausal women.

Abnormal uterine bleeding, pelvic pain and pressure, and a multitude of adverse reproductive outcomes are attributable to leiomyomas in up to 40 percent of women over age 35, causing significant impairment in their quality of life.

Leiomyomas are composed of abundant extracellular matrix, including collagen and versican, a large proteoglycan, rendering them fibrotic. While the precise molecular mechanism of leiomyoma development is not well-understood, leiomyoma growth is known to be dependent on estrogen and progesterone, as well as these hormones’ respective receptors, ESR1 and PR-A.

We investigated the impact of versican and its fragments on the behavior of leiomyoma and whether versican proteolysis in leiomyomas could help explain the pathogenesis of this disease, and perhaps offer new therapeutic directions. Members of the Ob/Gyn & Women’s Health Institute and the Biomedical Engineering Department, Lerner Research Institute, undertook an investigation of ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protease-mediated versican cleavage in myometrium and leiomyoma in symptomatic and asymptomatic women, as well as in immortalized myometrial and leiomyoma cell lines. Our study was published in The Journal of Clinical Endocrinology & Metabolism.¹

Tissue samples were collected from 14 women age 43-60 who underwent a hysterectomy between January 2015 and February 2016. Women in both groups were similar in age, race, parity and menopausal status. Asymptomatic women in the study had undergone hysterectomies for urinary incontinence and pelvic organ prolapse. Histology, and RNA and protein analyses were performed.

Versican is expressed in myometrium, leiomyoma

The women in the symptomatic group had larger leiomyomas, heavy menstrual bleeding and lower hemoglobin levels compared with the asymptomatic group, but were similar in age and menopausal status. Versican isoforms were upregulated in the leiomyomas of symptomatic versus asymptomatic women. Abundant cleaved versican was detected in leiomyomas and myometrium, as well as in myometrial and leiomyoma cell lines. Knockdown of versican in leiomyoma cells did not affect cell proliferation, apoptosis or smooth muscle markers, but reduced expression of the sex hormone receptors ESR1 and PR-A.

Therefore, we conclude that versican present in myometrium, leiomyomas and in the corresponding immortalized cells is cleaved by ADAMTS proteases. Furthermore, when versican is suppressed, essential hormone receptors contributing to the pathogenesis of leiomyoma (ESR1 and PR-A) are downregulated.

These findings illustrate the important role of versican and its effect in extracellular matrix-dependent leiomyoma growth. Future studies are needed to determine whether altering versican expression or cleavage offers a potential nonhormonal therapeutic approach for leiomyoma.

ABOUT THE AUTHORS

Dr. Gueye completed a reproductive endocrinology and infertility fellowship in the Ob/Gyn & Women’s Health Institute. Dr. Falcone is Chairman. Drs. Mead and Apte and Mr. Koch are with the Biomedical Engineering Department, Lerner Research Institute. Dr. Biscotti is on staff in the Anatomic Pathology Department.

Battling Weight Gain Together in Cyberspace

By Karen Cooper, DO

Innovative approach to a common problem

Cleveland Clinic’s Ob/Gyn & Women’s Health Institute is at the forefront of the telemedicine revolution, pioneering a shared medical appointment (SMA) combined with virtual visits for weight management.

SMAs: a record of success

During SMAs, patients with similar health issues — diabetes, hypertension, coronary artery disease or unwanted weight gain — meet as a group with healthcare providers. Sessions typically include a private portion for examinations.

SMAs have been shown to improve access, reinforce compliance, increase educational awareness and incubate a supportive patient environment. Data from studies in the mid-1990s by Kaiser Permanente in Colorado demonstrate reduced costs, decreased hospitalizations and improved patient and provider satisfaction with the use of SMAs.

Similar meetings for overweight and obesity management, i.e., Weight Watchers®, have proved advantageous by enhancing motivation and accountability, two areas in which patients struggle the most when trying to lose weight.

Adding a virtual component

In a traditional medical setting, such frequent monitoring is unfortunately not time- or cost-effective for providers or patients. We recognized that conducting meetings virtually could help overcome these obstacles.

Our virtual SMA (VSMA) pilot program involved a cohort of seven patients, all with initial body mass indexes between 30 and 45 kg/m². The first meeting was conducted in-person in the office.

Weight, vital signs and clinical history were recorded privately by a nurse or medical assistant. A dietitian explained the ketogenic diet, and a distance health program manager taught participants how to utilize mobile devices to join future virtual visits. We chose the ketogenic diet because it produces effective and efficient weight loss.

Each weekly follow-up VSMA lasted 45-60 minutes with four patients maximum. Individuals dialed in on Skype or FaceTime® from their smartphone, tablet or computer equipped with a camera. Practitioners interacted with patients on a widescreen monitor in the office, and patients could see us and one another on their devices.

Patients self-reported weights and shared thoughts, concerns, difficulties, triumphs and suggestions. Final weights were captured at the sixth and final visit, which was in-office.

VSMA results are excellent

Our first cohort achieved a combined weight loss of approximately 145 pounds over six weeks. Our biggest loser shed 33 pounds and dramatically lowered her blood pressure. Another lost 22 pounds despite a vacation. All patients increased exercise frequency to three to five times per week for 30-60 minutes.

Participants reported that VSMAs were highly motivating and inspiring, and expressed strong appreciation for frequent access to a physician at convenient times and for group support. All voiced the desire to continue the diet plan to meet their weight-loss goals.

Program launching

Insurance plans do not yet cover VSMAs, a hurdle for many patients despite the lower price point we established. However, based on the success of the pilot, we are launching a 12-week VSMA program for weight management.

We feel that VSMAs represent a new model of care with tangible advantages for health issues such as weight management.

Institute administrator Chad Kunkle helped develop the program.

ABOUT THE AUTHOR

Dr. Cooper is a staff member and Director of the Women’s Weight Management Program in the Ob/Gyn & Women’s Health Institute. She can be reached at 216.636.5027 or cooperk@ccf.org.
Two New Volumes by Cleveland Clinic Experts on Ob/Gyn Topics

**Operative Techniques in Gynecologic Surgery: Gynecology**, edited by Tommaso Falcone, MD, and associate editors, M. Jean Uy-Kroh, MD, and Linda D. Bradley, MD

The first in a new four-volume series, *Operative Techniques in Gynecologic Surgery: Gynecology* provides authoritative guidance on operative techniques, procedure selection, how to avoid complications and expected outcomes. Superbly illustrated and easy to follow, this step-by-step reference covers common gynecological procedures.

Each clinical problem is discussed in the same format: general principles, anatomy and differential diagnosis, imaging and other diagnostics, preoperative planning, surgical management, procedures and techniques, pearls and pitfalls, postoperative care, outcomes, and complications. The text is published by Lippincott Williams & Wilkins, part of Wolters Kluwer.

“We hope this new book serves as an easy-to-use reference tool for colleagues worldwide, ideal for both residents and physicians in daily practice,” Dr. Falcone says. “We thank our colleagues around the globe who contributed valuable information and chapters.”


This completely revised and expanded, user-friendly textbook covers polycystic ovary syndrome; pubertal disorders; amenorrhea; menopause; management of endometriosis and fibroids (including interventional radiology); and laboratory and clinical aspects of assisted reproductive technologies.

The update includes new chapters on osteoporosis, contraception and sterilization among other topics, and it expands the female infertility and fertility chapters to include information on preimplantation diagnosis and screening. The work is published by Springer International Publishing AG.

“Many advancements have been made in reproductive medicine since the last edition of this book was published in 2013,” Dr. Falcone says. “It was time for an update to this seminal textbook.”

Dr. Falcone, Chairman of the Ob/Gyn & Women’s Health Institute at Cleveland Clinic, has authored more than 500 original manuscripts, abstracts and book chapters and co-edited and edited several textbooks and patient handbooks. He serves on the editorial board and is an ad hoc reviewer of many journals, most notably *Fertility & Sterility* and *Obstetrics & Gynecology*. 