Ob/Gyn & Women’s Health Research Perspectives

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

Multicenter Trial of Single-Incision ‘Mini-Sling’ for Stress Urinary Incontinence

Ovarian Tissue Transplantation Shows Promise

OptumHealth Again Recognizes Cleveland Clinic Infertility Program

Study Evaluates Novel Surgical Robots in Gynecologic Oncology
CONTENTS

3 Cleveland Clinic Leads Multicenter Trial of Single-Incision ‘Mini-Sling’ for Stress Urinary Incontinence
4 Ovarian Tissue Transplantation Shows Promise
5 Falcone Editor of New Book
6 OptumHealth Again Recognizes Cleveland Clinic Infertility Program
6 A Tribute to Lawrence Levy, MD
7 Study Evaluates Novel Surgical Robots in Gynecologic Oncology
8 Clinical Trials
10 Selected Publications

Dear Colleagues & Friends:

Welcome to this the latest issue of Cleveland Clinic’s Ob/Gyn & Women’s Health Research Perspectives. We are pleased to share a few examples of the exciting work being conducted here.

Like prior editions of this publication, this edition is intended to give you a sample of the path-breaking research being conducted in single-port robotic surgery, ovarian tissue transplantation and more. In addition, we are pleased to share some examples of excellence – in our programs, our physician professional leadership activities and our research scholarship.

We also recognize the life of the late Dr. Lawrence Levy and highlight some of the dozens of comments posted online from his patients, proving once again that the human touch is as significant to patients as cutting-edge medical advances.

While always a leader in the nation in numerous specialties, we are also close to home for our patients, as demonstrated by the expansion of our reach to Family Health Centers, and look forward to three additional sites coming online this year.

For information on how efficiently we care for our patients, please review the most recent edition of Cleveland Clinic’s Outcomes, available at clevelandclinic.org/quality/outcomes.

We hope that you will find this issue valuable and inspiring. Please feel free to contact us with suggestions and questions – we look forward to the collaborative possibilities those interactions may bring.

Sincerely,

Tommaso Falcone, MD  Matthew Barber, MD
Professor & Chairman,  Vice Chairman, Clinical Research
Department of Obstetrics and Gynecology  Ob/Gyn & Women’s Health Institute

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In spite of those methods’ proven efficacy, relative safety and widespread adoption, the blind trocar passage through the retropubic or transobturator space required for standard mid-urethral sling placement is a concern for some surgeons. In response to this, several companies introduced smaller, less invasive slings that could be placed through a single sub-urethral incision in an effort to eliminate this blind trocar passage. As such, there is the potential with these devices for fewer complications, less postoperative pain and decreased anesthesia requirements than with standard slings. However, the relative efficacy and safety of the mini-slings have not been well-studied.

In 2007, Cleveland Clinic’s Center for Urogynecology and Reconstructive Pelvic Surgery received a grant from the Foundation for Female Health Awareness (femalehealthawareness.org) to conduct a multicenter randomized trial on the use of the two devices. The study compares a single-incision mini-sling (TVT-SECUR, manufactured by Ethicon Women’s Health and Urology) to the current “gold standard” mid-urethral sling, the tension-free vaginal tape or TVT, in the SECURiTy trial.

The TVT-SECUR can be implanted using a retropubic “U” approach or a transobturator-like “hammock” approach. This is the first study to compare the “U” approach to a standard retropubic mid-urethral slings such as the TVT. Cleveland Clinic was the Data Coordinating Center for this study and one of seven sites in the U.S. that recruited patients with stress-predominant urinary incontinence for this trial.

Two hundred and eighty-one participants were enrolled in the trial, and follow-up continued for a mean of 18 months. While TVT-SECUR demonstrated several advantages over TVT, including fewer bladder perforations, decreased pain in the first three days after surgery and lower rates of postoperative catheterization, the severity of urinary incontinence after surgery was greater with TVT-SECUR than with TVT.

One year after surgery, the rate of “cure,” defined as the absence of any urinary incontinence symptoms or re-treatment, was similar between treatment groups (TVT-SECUR 57 percent vs. TVT 60 percent). However, incontinence severity at one year was greater with TVT-SECUR than with TVT, resulting predominantly from a higher proportion of subjects with “severe” incontinence postoperatively: 16 percent vs. 5 percent, p=.026. Retreatment for stress incontinence occurred in 1.5 percent and 2.4 percent of subjects, respectively.

The results of the SECURiTy trial were presented at the 2011 International Urogynecological Association Meeting in Lisbon, Portugal, in June 2011, where the paper received the Axel Ingelman-Sundberg Award for Best Abstract. The results will be presented at the 2011 Annual Meeting of the American Urogynecological Society in Providence, R. I., in September.

Cleveland Clinic’s Center for Urogynecology and Pelvic Reconstructive Surgery has long focused on performing clinical trials in an effort to identify the best treatments for these conditions. We are currently participating in a number of other clinical trials evaluating the surgical treatment of urinary incontinence and pelvic organ prolapse (my.clevelandclinic.org/ob_gyn/physicians/clinicaltrials.aspx).

Dr. Barber is Professor and Vice Chairman for Clinical Research of the Ob/Gyn & Women’s Health Institute. Physicians may reach him at 216.445.0439 or barberm2@ccf.org.
Ovarian Tissue Transplantation Shows Promise

By Tommaso Falcone, MD

Women undergoing potentially gonadotoxic chemotherapy have several options for preserving fertility. Cleveland Clinic offers traditional methods, including in vitro fertilization and embryo freezing, and is actively involved in research into experimental approaches.

One option is to obtain ovarian tissue surgically and cryopreserve it. When the patient is ready to conceive, she would have two ways to utilize the tissue. The first is to thaw and grow the oocytes in vitro from a primordial stage.

In humans, in vitro culture and maturation time may be as long as six months, depending on follicle size at isolation. Unfortunately, none of the existing culture systems are ideal for in vitro culture and maturation of follicles over such extended time periods. In traditional 2-D culture systems, the follicles tend to flatten out as granulosa cells attach and grow as a monolayer. The in vivo spherical structure is quickly lost and the very important and fragile communication links between the oocyte and the granulosa cells often become disrupted before oocyte maturation has been completed.

The other hurdle has been determining the in vitro culture requirements for the follicle and its enclosed oocyte. Clearly, in the absence of in vivo signaling and growth factor/cytokine exposure, designing the appropriate culture milieu is paramount to successful in vitro maturation.

The other option is to transplant the tissue back into the ovarian site. The longevity of the graft is compromised because it takes 48-72 hours to grow a new microscopic blood supply. During this ischemic time, the oocytes may be destroyed.

Our research has looked into how we can accelerate this process. The results, published recently in the journal *Fertility & Sterility*, describe our efforts to determine if granulocyte colony-stimulating factor (G-CSF), stem cell factor (SCF) and vascular endothelial growth factor (VEGF) improve outcome of ovarian grafting. We used a mouse model when conducting this research.

Transplanted ovaries in mice injected with VEGF concurrently with G-CSF maintained a significantly larger pool of primordial follicles compared with transplanted ovaries in saline-injected controls. Follicle numbers (total immature and primordial) in transplanted ovaries did not differ significantly in mice injected with VEGF alone or G-CSF plus SCF compared with saline-injected controls.

We concluded that treatment of mice after ovarian transplantation with VEGF and G-CSF maintains a significantly greater number of primordial follicles compared with transplanted ovaries in control animals, suggesting that a combination of G-CSF and VEGF minimizes ischemic damage and thus improves viability and function of the ovarian graft.

This research suggests that frozen-thawed ovary transplantation may be a viable approach to preserve fertility in women in the future.

Dr. Falcone is Professor and Chairman of the Ob/Gyn & Women’s Health Institute. Physicians may reach him at 216.444.1758 or falconet@ccf.org.
Falcone Editor of New Book

Dr. Tommaso Falcone recently edited, with Drs. David Gardner and Botros Rizk, *Human Assisted Reproductive Technology: Future Trends in Laboratory and Clinic Practice*. The collection of reviews was published by the medical division of Cambridge University Press.

The publication offers a collection of concise, practical review articles on cutting-edge topics within reproductive medicine. Each article presents a balanced view of clinically relevant information and looks ahead to how practice will change over the next five years.

For more information or to purchase the book, visit Amazon.com.

Excellent follicle survival after transplantation and the use of vascular endothelial growth factor (VEGF) and granulocyte colony-stimulating factor (G-CSF).
OptumHealth Again Recognizes Cleveland Clinic Infertility Program

Cleveland Clinic Women’s Health Institute continues to meet criteria as a designated Center of Excellence under OptumHealth’s Reproductive Resource Services program.

Physicians at Cleveland Clinic have more than 5,700 annual patient visits for infertility-related issues and services alone. A multidisciplinary team from the Glickman Urological & Kidney Institute and the Ob/Gyn & Women’s Health Institute addresses the fertility needs of both men and women, delivering personalized treatment options for every couple, including artificial insemination, ovulation induction, intracytoplasmic sperm injection, in vitro fertilization and preimplantation genetic diagnosis. From a surgical perspective, Cleveland Clinic aims to preserve fertility with minimally invasive techniques whenever possible, including robotic surgery, single-port surgery, microsurgery and advanced endoscopic techniques for women with advanced endometriosis.

Lawrence Levy, MD

The Cleveland Clinic family recently mourned the loss of Lawrence Levy, MD. Dr. Levy passed away April 21.

Dr. Levy was a dedicated breast surgeon for nearly 25 years. Before joining the General Surgery Department at Cleveland Clinic in 1997 as a breast surgeon, he was Head of the Section of Breast Surgery at Mt. Sinai Medical Center in Cleveland, where he began his career as an obstetrician/gynecologist and did both his internship and residency. Dr. Levy was an obstetrician/gynecologist for 25 years.

He was also an Assistant Clinical Professor at Cleveland Clinic Lerner College of Medicine. Dr. Levy enjoyed teaching medical students and residents and was a gifted educator.

Patients remember Dr. Levy fondly.

“He was a skilled physician and a wonderful human being. He was my gynecologist and later my surgeon,” comments one patient online. “He was warm, caring and a fierce advocate. The care he provided me is my benchmark for dealing with all physicians.”

Levy, a New York City native, earned a bachelor’s degree from The Ohio State University and his medical degree from Western Reserve University after a two-year stint in the U.S. Army.

While in college, he began a long tradition of participation in research and professional organizations, winning awards and serving as principal investigator on numerous research projects. He held leadership positions at both hospitals where he spent his long career, as well as with the local chapter of the American Cancer Society and The Gathering Place.

“I’ve never met a gentler human being,” comments another patient. “He was a doctor who treated so many women in my family for breast cancer – saving their lives and so many others … I will think of Larry every time I get to partner up with my mom on the tennis court, make plans with my aunt for dinner and enjoy his gift of more time with some of the people I love most.”

OptumHealth’s Centers of Excellence networks are considered the gold standard in complex healthcare. In 1986, the OptumHealth Transplant Centers of Excellence network was launched and has grown to be the largest network of its kind in the world, managing more than 11,000 transplant referrals each year. Today, products and services that promote safe, successful and cost-effective treatment options for many other complex medical conditions, including cancer, congenital heart disease and infertility, are recognized with the organization’s Centers of Excellence designation.
Innovations in minimally invasive surgical technology have allowed surgeons to perform increasingly complex surgeries through smaller incisions. An emerging area in minimally invasive surgery is single-port laparoscopy (SPL), or laparoendoscopic single-site surgery (LESS). SPL entails performing laparoscopic surgery utilizing a multichannel port system, typically placed through a single umbilical skin incision. New technologies have improved the success and reproducibility of these single-access approaches, including the use of flexible laparoscopes, flexible instruments and internal retractors.

While the LESS approach is innovative and may be the newest frontier in laparoscopic surgery, Cleveland Clinic surgeons say it presents unique challenges, including instrument crowding, loss of depth perception and a need for advanced laparoscopic skills. The Ob/Gyn & Women’s Health Institute Section of Gynecologic Oncology currently is evaluating novel surgical single-port robots to overcome the aforementioned limitations. Research in this area has been sponsored by the Department of Ob/Gyn & Women’s Health Institute and the Fund for Research in Minimally Invasive Gynecologic Oncology.

In September 2009, Cleveland Clinic reported the first robotic-assisted single port gynecologic procedure after successfully completing a hysterectomy on a 68-year-old woman [1]. The case was performed through one 2.5-cm incision in the umbilicus, and utilizing the existing robotic multiport platform enhanced cosmetic result and reduced morbidity. Further advancement in instrumentation has allowed Cleveland Clinic Oncologists to evaluate novel single-incision robotic platforms.

In March 2011, Dr Escobar reported in the journal Gynecologic Oncology the first preclinical study on the evaluation of a novel single-port robotic platform for the performance of various procedures in gynecologic oncology [2]. This preliminary data demonstrated that the performance of various oncology procedures using the new single-site robotic platform is feasible, and, more important, reproducible in the preclinical model. Further clinical studies are ongoing in this promising area of surgical research.

Dr. Escobar is Assistant Professor of Surgery and Director of Laparoscopy and Robotic Surgery of the Ob/Gyn & Women’s Health Institute. Physicians may reach him at 216.445.8486 or escobap@ccf.org.

REFERENCES


Cleveland Clinic has a robust research program in gynecologic cancers. For more information, call 216.445.8090.

BENIGN TRIALS

Title: Pregabalin for the Treatment of Vulvodynia: Randomized Double-Blinded Placebo Controlled
IRB: 08-195
Treatment: Vulvar Disease
Status: Open
Principal Name: Beri Ridgeway, MD
Research Line: 216.445.8090

Title: A New Condition-Specific Quality of Life Scale for Women With Vulvovaginal Pain Disorders ACOG
IRB: 8404
Treatment: Vulvar Disease
Status: Open
Principal Name: Eric Jelovsek, MD
Research Line: 216.445.8090

Title: Lower Urinary Tract Symptom Evaluation of Women With Uterine Leiomyomata (LOTUS)
IRB: 09-923
Treatment: Uterine Fibroids
Status: Open
Principal Name: Tyler Muffly, MD
Research Line: 216.445.8090

Title: Prevention of Catheter-Associated Urinary Tract Infection in Incontinence and Reconstructive Pelvic Surgery (PRECAUTION)
IRB: 10-125
Treatment: Reconstructive Pelvic Surgery
Status: Open
Principal Name: Ellen Solomon, MD
Research Line: 216.445.8090

Title: Assessment of Voiding After Sling (AVAS): A Randomized Trial of Two Methods of Postoperative Catheter Management After Midurethral Sling for Female Stress Urinary Incontinence
IRB: 11-082
Treatment: Stress Incontinence
Status: Open
Principal Name: Elena Tunitsky-Bitton, MD
Research Line: 216.445.8090

Title: Vaginal Uphold Hysteropexy and Laparoscopic Sacral Hysteropexy for the Treatment of Uterovaginal Pelvic Organ Prolapse: A Parallel Cohort Study (VaULT)
IRB: 11-409
Treatment: Pelvic Organ Prolapse
Status: Open
Principal Name: Matthew Barber, MD
Research Line: 216.445.8090

Title: Refractory Overactive Bladder: Sacral Neuromodulation vs. Botulinum Toxin Assessment (ROSETTA)
IRB: Pending
Treatment: Urge Incontinence
Status: Not currently open
Principal Name: Sandip Vasavada, MD
Sponsor: NICHD Pelvic Floor Disorders Network
Research Line: 216.445.8090

ONCOLOGY TRIALS

Title: GOG0213 A Randomized Controlled Clinical Trial of Platinum-Combination, Sequence-Dependent Chemotherapy and Secondary Cytoreductive Surgery in Platinum-Sensitive, Recurrent Ovarian and Peritoneal Primary Cancer
IRB: CC444
Treatment: Ovarian Cancer
Status: Open
Principal Name: Peter Rose, MD
Research Line: 216.445.8090

Title: GOG0240 A Randomized Phase III Trial of Cisplatin Plus Paclitaxel With and Without NCI-Supplied Bevacizumab vs. the Non-Platinum Doublet, Topotecan Plus Paclitaxel, With and Without NCI-Supplied Bevacizumab, in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix
IRB: CC724
Treatment: Cervical Cancer
Status: Open
Principal Name: Peter Rose, MD
Research Line: 216.445.8090

Title: GOG0249 A Phase III Trial of Pelvic Radiation Therapy Versus Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin Chemotherapy in Patients With High-Risk, Early-Stage Endometrial Carcinoma
IRB: CC699
Treatment: Endometrial Cancer
Status: Open
Principal Name: Peter Rose, MD
Research Line: 216.445.8090
Title: GOG0250 A Randomized Phase III Evaluation of Docetaxel (NSC#628503) and Gemcitabine (NSC#613327) Plus G-CSF With Bevacizumab (NSC#704865, IND#7921) Versus Docetaxel (NSC#628503) and Gemcitabine (NSC#613327) Plus G-CSF With Placebo in the Treatment of Recurrent or Advanced Leiomyosarcoma of the Uterus  
IRB: CC852  
Treatment: Uterine Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG0252 Phase III Clinical Trial of Bevacizumab with IV versus IP Chemotherapy in Ovarian, Fallopian Tube and Primary Peritoneal Carcinoma  
IRB: CC778  
Treatment: Ovarian Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG0258 A Randomized Phase III Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Advance Endometrial Cancer  
IRB: CC735  
Treatment: Endometrial Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG0261 A Randomized Phase III Trial of Paclitaxel Plus Carboplatin vs. Ifosfamide Plus Paclitaxel in Chemotherapy Naive Patients With Newly Diagnosed Stage I-IV, Persistent or Recurrent Carcinosarcoma of the Uterus or Ovary  
IRB: CC822  
Treatment: Uterine/Ovarian Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG0263 Randomized, Phase III Clinical Trial of Adjuvant Radiation Versus Chemoradiation in Intermediate Risk, Stage I/IIA Cervical Cancer Treatment With Initial Radical Hysterectomy and Pelvic Lymphadenectomy  
IRB: CC968  
Treatment: Cervical Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG9918 Phase I Trial of Tailored Radiation Therapy With Concomitant Cetuximab (C225, NSC #74692) and Cisplatin (NSC #119875) in the Treatment of Patients With Cervical Cancer  
IRB: 8042  
Treatment: Cervical Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: GOG9923 A Phase I Study of Carboplatin/Paclitaxel and CTEP-Supplied Bevacizumab (NSC #704865, IND #7921) and CTEP-Supplied ABT-888 (NSC #737664, IND #77840) in Newly Diagnosed Patients With Previously Untreated Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer  
IRB: CC853  
Treatment: Cervical Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: An Open-label, Single-Arm, Multicenter Phase 2 Study of E7080 in Subjects With Advanced Endometrial Cancer and disease Progression Following First-line Chemotherapy  
IRB: CC998  
Treatment: Endometrial Cancer  
Status: Open  
Principal Name: Richard Drake, MD  
Research Line: 216.445.8090

Title: A Randomized, Open-label Phase II Trial of Maintenance Therapy With a MUC1 Dendritic Cell Vaccine (Cvac) for Epithelial Ovarian Cancer Patients in First or Second Remission  
IRB: CC918  
Treatment: Ovarian Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of MORAb-003 (farletuzumab) in Combination With Paclitaxel Therapy in Subjects With Platinum-Resistant or Refractory Relapsed Ovarian Cancer  
IRB: CC922  
Treatment: Ovarian Cancer  
Status: Open  
Principal Name: Peter Rose, MD  
Research Line: 216.445.8090

Below is the direct URL for a complete list of gynecologic trials on the public Cleveland Clinic website (updated daily).  my.clevelandclinic.org/cancer/clinical_trials/trialresults.aspx?disease=gynecologic


Rose PG, Monk BJ, Provencher D, Hartney J, Legenne P, Lane S. An open-label, single-arm Phase II study of intravenous weekly (Days 1 and 8) topotecan in combination with carboplatin (Day 1) every 21 days as second-line therapy in patients with platinum-sensitive relapsed ovarian cancer. Gynecol Oncol 2011;120(1):38-42.


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Obstetrics & Gynecology
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On the Web at
clevelandclinic.org/obgyn

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Cleveland Clinic’s Gynecology program is ranked No. 4 in the nation by U.S. News & World Report.

PHYSICIAN DIRECTORY  View all Cleveland Clinic staff online at clevelandclinic.org/staff. To request a printed version of the Ob/Gyn directory, call Susan Anton at 216.448.1020.

CRITICAL CARE TRANSPORT WORLDWIDE  Cleveland Clinic’s critical care transport team serves critically ill and highly complex patients around the globe. Critical care transport is available for children and adults.

To arrange a transfer for STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndromes, call 877.379.CODE (2633). For all other critical care transfers, call 216.444.8302 or 800.553.5056.

IMPROVED COMMUNICATION, IMPROVED CARE  DrConnect offers secure access to your patient’s treatment progress at Cleveland Clinic. To establish a DrConnect account, visit clevelandclinic.org/drconnect or email drconnect@ccf.org.

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OUTCOMES DATA AVAILABLE  Our Outcomes books contain clinical outcomes data and information on volumes, innovations, research and publications. To view Outcomes books for many Cleveland Clinic institutes, visit clevelandclinic.org/outcomes.