The Role of Corin and ANP in Adverse Pregnancy Outcomes

 ALSO IN THIS ISSUE

OPTIMAL Trial: Outcomes for Two Vaginal Prolapse Surgical Repairs

Post-laparoscopy COH+IUI for Endometriosis

Adverse Events After Minimally Invasive Abdominal Sacrocolpopexy
Dear Colleagues and Friends:

While basic research is the bedrock on which all medical advances are built, Cleveland Clinic also focuses heavily on translational research — moving discoveries from the lab bench to the patient's bedside, where their application can do the greatest good.

In last summer's edition of *Ob/Gyn & Women's Health Research Perspectives*, we detailed a provocative study by Qingyu Wu, MD, PhD, and colleagues at Cleveland Clinic's Lerner Research Institute. Dr. Wu and his collaborators identified a new function for the cardiac protease corin: promoting the trophoblast invasion and spiral artery remodeling that are essential for boosting uteroplacental blood flow in pregnancy. Dr. Wu's group also found corin gene mutations in preeclamptic patients, suggesting that defects in the function of corin and the blood pressure-regulating hormone atrial natriuretic peptide (ANP) that corin activates may contribute to preeclampsia.

Anjalika Gandhi, a medical student at Cleveland Clinic Lerner College of Medicine, wondered if Dr. Wu's groundbreaking findings could be put to use in clinical obstetrics, where there remains a great need for a biomarker or group of markers to indicate which patients will develop preeclampsia. Ms. Gandhi, as you'll read in these pages, is working with Uma Perni, MD, of our Department of Obstetrics to study levels of serum corin and ANP in women during their pregnancies. Their findings should shed further light on the enzyme's and hormone's potential for predicting preeclampsia. It's a good illustration of the powerful synergy between basic and translational research.

Elsewhere in *Research Perspectives*, you'll find more examples of our staff's efforts to reduce uncertainty and improve outcomes in the treatment of ob/gyn patients. We report on the OPTIMAL trial's comparison of the two most frequently performed vaginal prolapse surgical repairs; examine adverse events following robotic versus laparoscopic sacrocolpopexy; and evaluate the impact of controlled ovarian hyperstimulation and intrauterine insemination on pregnancy rates.

We hope you enjoy reading these accounts of the exciting research underway at the Ob/Gyn & Women's Health Institute. Please contact us with questions and suggestions. We welcome those interactions and the possibilities for future collaboration.

Sincerely,

Tomaso Falcone, MD, FRCSC, FACOG
Professor & Chairman,
Department of Obstetrics and Gynecology
Chairman, Ob/Gyn & Women's Health Institute

Matthew Barber, MD, MHS
Vice Chairman, Clinical Research
Ob/Gyn & Women's Health Institute
Preeclampsia is a syndrome in which reduced uteroplacental perfusion is associated with widespread endothelial dysfunction and often fetal growth restriction. Primary clinical features include hypertension, proteinuria, edema, and at times end organ dysfunction including elevated liver enzymes, thrombocytopenia, pulmonary edema and seizures. The primary cause of preeclampsia remains elusive, but impaired trophoblast invasion and spiral artery remodeling are thought to be involved in the pathogenesis of preeclampsia.

In normal early pregnancy, trophoblast cells from the developing placenta invade the endometrium and myometrium and migrate along the spiral arteries, transforming them into large-diameter conduit vessels of low resistance. This physiological transformation allows for greater blood flow to the growing fetus and is required for a successful pregnancy.

Failure of trophoblast invasion and spiral artery transformation has been documented in preeclampsia and in pregnancies complicated by intrauterine growth restriction (IUGR). Thus, failure of the spiral arteries to undergo physiological transformation allows for greater blood flow to the growing fetus and is required for a successful pregnancy.

In a recent Nature study, Cleveland Clinic researcher Dr. Qingyu Wu reported the discovery of a novel function of corin and atrial natriuretic peptide (ANP) in promoting trophoblast invasion and spiral artery remodeling. Corin is a cardiac protease that activates ANP, a cardiac hormone involved in the complex pathway of blood pressure regulation. Lack of corin in mouse models causes hypertension. In humans, genetic variants of corin are associated with high blood pressure. Unexpectedly, corin was also detected in the pregnant uterus, suggesting a possible function in pregnancy. Using transgenic mouse models, cell-based experiments with human trophoblasts and Matrigel™ matrices, as well as serum of preeclamptic women, Dr. Wu and his team reported the role of corin and ANP in promoting trophoblast invasion and spiral artery remodeling and in preventing hypertension in pregnancy. The data suggest that impaired corin expression or function in the pregnant uterus may represent an important mechanism underlying preeclampsia.

Genesis of Cohort Study

Reading this article stimulated Anjalika Gandhi, a fourth-year medical student at Cleveland Clinic Lerner College of Medicine, to ask how these groundbreaking basic science findings could be translated into the clinical realm to help patients. Clinically, a major challenge in the practice of obstetrics is to identify women who will develop preeclampsia. Despite significant research into potential biomarkers, no single marker or group of markers has been able to predict this condition.

Ms. Gandhi, who has worked with Cleveland Clinic’s Ob/Gyn & Women’s Health Institute in other research endeavors, formulated clinical research questions based on Dr. Wu’s findings. Together, we have designed a prospective cohort study of high-risk pregnant women to better understand the role of corin and the development of adverse pregnancy outcomes, including preeclampsia and IUGR.

Women with one or more risk factors for developing preeclampsia, including but not limited to chronic hypertension, pregestational diabetes, obesity or a prior history of preeclampsia, are approached for participation. Women who agree to participate have blood collected at two time points in their pregnancy for analysis.
Specifically, we are investigating early-pregnancy serum corin and ANP levels in women who develop preeclampsia and/or IUGR compared with those who do not. We will also include a small cohort of low-risk pregnancies for comparison.

Hypothesis and Goals

We hypothesize that in early pregnancy, serum corin and ANP levels will be decreased in women who develop preeclampsia and/or growth restriction secondary to the role of these proteins in early trophoblast invasion. We will also investigate the changes in these levels in late pregnancy to identify differences in these two groups. We plan to compare early and late levels in women who develop preeclampsia and require preterm delivery to early and late levels in women who develop preeclampsia and deliver at term.

Our final question will be whether including corin and ANP as predictive markers improves the predictive capability of other well-studied markers such as placental growth factor.

The study is funded by a grant from Cleveland Clinic’s Research Program Committee. Statistical analyses will be aided by Benjamin Nutter from the Lerner College of Medicine Department of Quantitative Health Sciences.

Recruitment took place from September 2013 to March 2014, with 133 patients enrolled. Final pregnancy outcomes are expected by September, with final results by October 2014.

Dr. Perni is an associate staff member of the Department of Obstetrics in Cleveland Clinic’s Ob/Gyn & Women’s Health Institute. She can be reached at 440.312.2229 or perniu@ccf.org.

Study Results

Peri- and postoperative outcomes for patients undergoing either RSC or LSC without concomitant rectopexy are displayed in Table 1. RSC cases were associated with a higher intraoperative bladder injury rate (3.3 percent [95 percent confidence interval 1.3-8.2] vs. 0.4 percent [95 percent CI 0.07-2.2], p = 0.04). RSC was also associated with a higher rate of estimated blood loss (EBL) of ≥ 500 mL (2.5 percent [95 percent CI 0.8-7.0] vs. 0 percent, p = 0.01). Otherwise, there were no statistical differences in peri- and postoperative outcomes between the two groups.

While efficacy outcomes data do exist, there are currently no large studies that compare peri- and postoperative adverse events of sacrocolpopexy performed robotically or with conventional laparoscopy. Our study’s primary objective was to compare peri- and postoperative adverse events between RSC and LSC in a large cohort of women undergoing these procedures at Cleveland Clinic between 2006 and 2012. Secondary aims were to explore whether hysterectomy and rectopexy at the time of sacrocolpopexy were specifically associated with these adverse events.

Four hundred six subjects met inclusion criteria. Mean age and body mass index of all subjects were 58 (± 10) years and 27.9 (± 4.9) kg/m², respectively. Two hundred sixty-one subjects underwent LSC and 145 subjects underwent RSC. 83.5 percent of subjects underwent concomitant pelvic organ prolapse (POP) or stress urinary incontinence procedures: 25.6 percent (104/406) of subjects underwent concomitant hysterectomy, 7.1 percent (29/406) anterior repair, 43.1 percent (175/406) posterior repair and 65 percent (264/406) midurethral sling placement. RSC subjects were older (60 ± 9 vs. 57 ± 10 years, p = 0.009) and more likely to be postmenopausal (90.9 percent vs. 79.1 percent, p = 0.05) compared with the LSC group. Concomitant hysterectomy and rectocele repair were more common with LSC patients compared with the RSC cases: 28.7 percent vs. 20 percent, p = 0.05, and 48.7 percent vs. 33.1 percent, p = 0.002, respectively.

Perioperative Adverse Events After Minimally Invasive Abdominal Sacrocolpopexy

By Cecile Unger, MD, MPH

Robot-assisted laparoscopic sacrocolpopexy (RSC) and conventional laparoscopic sacrocolpopexy (LSC) have become alternatives to the open abdominal approach to sacrocolpopexy. These procedures aim to bridge the gap between the advantages of vaginal surgery — namely decreased morbidity and faster patient recovery — and the surgical success rates of abdominal sacrocolpopexy.
Perioperative Adverse Events After Minimally Invasive Abdominal Sacrocolpopexy

By Cecile Unger, MD, MPH

CI 0.05-1.5), p = 0.04), cardiac-related complications (5.6 percent [95 percent CI 1.5-18.1] vs. 0.8 percent [95 percent CI 0.3-2.4], p = 0.01), and pelvic/abdominal abscess formation (11.1 percent [95 percent CI 4.4-25.3] vs. 0.8 percent [95 percent CI 0.3-2.4], p < 0.001). Rectopexy was also associated with a higher risk of osteomyelitis (5.6 percent [95 percent CI 1.5-18.1] vs. 0 percent, p < 0.001).

Median follow-up for all patients was 195 days [Interquartile Range 73.5-427] and was not different between RSC and LSC: 205 [87-432] vs. 191 [61-420], p = 0.72.

Vaginal mesh erosion was experienced by 2.7 percent (11/406); 63.6 percent (7/11) of the erosions were related to the sacrocolpopexy and 36.4 percent (4/11) were midurethral sling mesh erosions with no difference between RSC and LSC.

Of the 10 subjects who underwent reoperation for POP, 80 percent (8/10) of the surgeries were for symptomatic rectocele, 20 percent (2/10) were for symptomatic cystocele and no subjects underwent reoperation for symptomatic apical prolapse. Of the 10 subjects who underwent reoperation, 70 percent (7/10) were RSC cases. Patients who underwent RSC were more likely to undergo reoperation for POP when compared with LSC cases (4.9 percent [95 percent CI 2.2-9.9] vs. 1.1 percent [95 percent CI 0.4-3.3], p = 0.02). Initial rectocele repair at the time of sacrocolpopexy was more common in the LSC group than the RSC group (48.7 percent [95 percent CI 42.7-54.7] vs. 33.1 percent [95 percent CI 26.0-41.1], p = 0.002). The rate of erosion was not statistically different for subjects who underwent concomitant hysterectomy (2.0 percent [95 percent CI 0.8-3.4] vs. 3.0 percent [95 percent CI 1.2-5.2], p = 0.65). Type of hysterectomy (supracervical vs. total) was not associated with mesh erosion.

Conclusions

Minimally invasive abdominal sacrocolpopexy confers many benefits compared with open abdominal sacrocolpopexy and has been shown to be comparable in terms of surgical outcomes. Overall peri- and postoperative complication rates appear to be low, with the exception of cases involving concomitant rectopexy. RSC appears to have a higher rate of bladder injury, EBL ≥ 500 mL and reoperation for recurrent POP when compared with LSC; otherwise, the two modalities appear similar in their adverse event rates.

Further research should be done to confirm these favorable and comparable rates, and to further investigate the risk of rectopexy at the time of sacrocolpopexy.

Dr. Unger is a Fellow in Cleveland Clinic’s Ob/Gyn & Women’s Health Institute. This study was presented at the Society of Gynecologic Surgeons’ 40th Annual Scientific Meeting and the Cleveland Society of Obstetricians and Gynecologists’ Annual Meeting. Dr. Unger’s collaborators for the study were Marie Fidelia R. Paraiso, MD; J. Eric Jelovsek, MD; Matthew D. Barber, MD, MHS; and Beri Ridgeway, MD, all of Cleveland Clinic’s Ob/Gyn & Women’s Health Institute. Dr. Unger can be reached at ungerc@ccf.org.

Table 1. Peri- and postoperative adverse events for LSC v. RSC without concomitant rectopexy

<table>
<thead>
<tr>
<th>Event</th>
<th>All Subjects N = 370</th>
<th>LSC N = 249</th>
<th>RSC N = 121</th>
<th>OR (95 %CI) (^*)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion to Open Abdominal</td>
<td>1.9 (0.9,3.9)</td>
<td>2.0 (0.9,4.6)</td>
<td>1.7 (0.5,5.8)</td>
<td>0.5 (0.1,1.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Bladder Injury</td>
<td>1.2 (0.5,2.9)</td>
<td>0.4 (0.07,2.2)</td>
<td>3.3 (1.3,8.2)</td>
<td>0.1 (0.02,0.93)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Urinary Injury</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bowel Injury</td>
<td>1.6 (0.7,3.5)</td>
<td>1.2 (0.4,3.5)</td>
<td>2.5 (0.8,7.0)</td>
<td>0.55 (0.1,2.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Vascular Injury</td>
<td>0.7 (0.3,2.1)</td>
<td>0.8 (0.2,2.9)</td>
<td>0.8 (0.1,4.5)</td>
<td>1.1 (0.1,12.4)</td>
<td>0.98</td>
</tr>
<tr>
<td>EBL ≥ 500 mL</td>
<td>1.0 (0.4,2.5)</td>
<td>0</td>
<td>2.5 (0.8,7.0)</td>
<td>0.2 (0.02,0.81)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Wound Infection</td>
<td>3.7 (2.3,6.0)</td>
<td>2.8 (1.4,5.7)</td>
<td>4.1 (1.7,9.3)</td>
<td>0.8 (0.3,2.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.7 (0.3,2.1)</td>
<td>1.2 (0.4,3.5)</td>
<td>0 (0)</td>
<td>–</td>
<td>0.23</td>
</tr>
<tr>
<td>Transfusion</td>
<td>0.5 (0.1,1.8)</td>
<td>0.4 (0.07,2.2)</td>
<td>0 (0)</td>
<td>0.6 (0.03,8.9)</td>
<td>0.49</td>
</tr>
<tr>
<td>Pelvic Abscess</td>
<td>0.8 (0.3,2.4)</td>
<td>0.8 (0.2,2.9)</td>
<td>0.8 (0.1,4.5)</td>
<td>1.4 (0.3,7.3)</td>
<td>0.98</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>0.5 (0.1,1.8)</td>
<td>0.8 (0.2,2.9)</td>
<td>0 (0)</td>
<td>–</td>
<td>0.32</td>
</tr>
<tr>
<td>Ileus</td>
<td>0.5 (0.1,1.9)</td>
<td>0.8 (0.2,2.9)</td>
<td>0 (0)</td>
<td>–</td>
<td>0.32</td>
</tr>
<tr>
<td>Bowel Obstruction</td>
<td>0.8 (0.3,2.4)</td>
<td>0.4 (0.07,2.2)</td>
<td>1.7 (0.5,5.8)</td>
<td>0.6 (0.08,4.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Neurologic Injury</td>
<td>3.5 (2.1,5.9)</td>
<td>3.6 (1.9,6.7)</td>
<td>3.3 (1.3,8.2)</td>
<td>1.3 (0.4,4.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.6 (0.7,3.5)</td>
<td>1.6 (0.6,4.1)</td>
<td>1.7 (0.5,5.8)</td>
<td>0.7 (0.2,3.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.8 (0.3,2.4)</td>
<td>0.8 (0.2,2.9)</td>
<td>0.8 (0.1,4.5)</td>
<td>0.8 (0.1,5.0)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mesh Erosion</td>
<td>2.7 (1.5,4.9)</td>
<td>2.4 (1.1,5.2)</td>
<td>3.3 (1.3,8.2)</td>
<td>0.3 (0.06,1.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Dindo Grade 3</td>
<td>26.3 (22.0,31.0)</td>
<td>26.4 (21.3,32.3)</td>
<td>26.1 (19.0,34.6)</td>
<td>1.0 (0.6,1.5)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Data unadjusted for baseline differences and presented as % (95 %CI)

\(^*\) = unadjusted odds ratio

\(*\) = statistically significant difference at \( \alpha = 0.05 \)

EBL = estimated blood loss

DVT/PE = deep vein thrombosis/pulmonary embolus

Dindo Grade 3 = requiring surgical, endoscopic or radiologic imaging/intervention (with or without anesthesia)
Post-laparoscopy COH+IUI for Endometriosis Does Not Improve Pregnancy Rates

Although operative laparoscopy has shown some ability to improve postoperative pregnancy rates in women with endometriosis-related infertility, the results remain suboptimal. Because of this, additional fertility interventions must be considered.

One postoperative option is controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI). Some clinicians advocate the use of COH + IUI before in vitro fertilization (IVF), due to the former procedure’s reduced cost and similar pregnancy rates compared with IVF. However, there is a lack of consensus as to how to proceed with persistent postoperative infertility, and the true success of COH + IUI after surgery remains unclear.

Researchers from Cleveland Clinic, the Cleveland Clinic Lerner College of Medicine and Sao Paulo University recently conducted a retrospective study to assess the effectiveness of COH + IUI after operative laparoscopy in all stages of endometriosis.

The results, published in the Journal of Minimally Invasive Gynecology, showed that COH + IUI did not improve pregnancy rates in any stage of endometriosis. The study’s lead author is Tommaso Falcone, MD, FRCSC, FACOG, Chairman of Cleveland Clinic’s Ob/Gyn & Women’s Health Institute.

Study Details

The retrospective study involved a statistical analysis of a cohort of patients diagnosed with infertility (defined as attempting pregnancy for more than 12 continuous months before surgery). Patients enrolled in the study were ages 18 to 35 when they underwent operative laparoscopy to treat endometriosis between 2001 and 2011 at Cleveland Clinic. Additional enrollment criteria were that patients had undergone assessment of at least one patient fallopian tube via hysterosalpingography or laparoscopic chromotubation.

No Advantage for COH + IUI

As reported in the Journal of Minimally Invasive Gynecology, among women with stage I/II endometriosis, there was no statistically significant difference in cumulative 12-month pregnancy rates of COH + IUI and spontaneous attempts (45 percent vs. 42 percent, p = 0.49). Patients with stage III/IV disease had 12-month cumulative pregnancy rates of 10 percent with COH + IUI and 31 percent with spontaneous attempts, a difference that was not statistically significant (p = 0.18).

The study results do not support COH + IUI at any stage of endometriosis, Dr. Falcone and his co-authors write. They recommend that patients with stage III/IV surgically treated endometriosis be allowed three to four months immediately postoperatively to attempt spontaneous pregnancy. If that is unsuccessful, the study’s authors do not recommend COH + IUI, but support IVF.

Patients with surgically treated stage I/II endometriosis age 35 or younger should attempt spontaneous conception for six to 12 months postoperatively, after which some, but not all, may benefit from three or four cycles of COH + IUI due to its potential to shorten the time to pregnancy, the authors concluded.

Though the study results have clinical significance and are generalizable, the study was limited by its retrospective nature, sample size, and possible selection and recall bias. Randomized clinical trials would verify and further clarify the findings.

For more information, contact Dr. Falcone at 216.444.1758 or falcont@ccf.org.
OPTIMAL Trial Finds Comparable Outcomes for Two Vaginal Prolapse Surgical Repairs, No Benefit for Behavioral Therapy

By Matthew Barber, MD, MHS

Vaginal prolapse and resultant stress urinary incontinence are a common post-childbirth complication, with approximately 300,000 prolapse surgeries performed annually in the United States.

Sacrospinous ligament fixation (SSLF) and uterosacral ligament vaginal vault suspension (ULS) are the two most frequently used procedures to correct apical vaginal prolapse. However, there have been no rigorous attempts to compare their relative efficacy and safety. Neither has there been an effort to determine whether perioperative behavioral therapy with pelvic floor muscle training (BPMT) — an effective stand-alone therapy for incontinence — improves the outcomes of prolapse surgery.

A multicenter trial known as OPTIMAL, for Operations and Pelvic Muscle Training in the Management of Apical Support Loss, sought to compare two-year outcomes of patients who underwent SSLF or ULS surgery for apical or uterine prolapse and stress urinary incontinence. The OPTIMAL trial, conducted at Cleveland Clinic and eight other U.S. medical centers between 2008 and 2013, also evaluated whether perioperative BPMT affected urinary symptoms six months after surgery, and whether it affected anatomic outcomes and prolapse symptoms 24 months after surgery.

OPTIMAL’s findings were that neither repair procedure was superior to the other for functional or adverse event outcomes. Also, the trial determined BPMT did not improve incontinence symptoms or prolapse outcomes.

Defining Successful Outcomes

OPTIMAL enrolled women 18 and older with complaints of vaginal bulge and stress urinary incontinence and undergoing surgery for stage 2 through 4 prolapse. Participants were randomly assigned to SSLF or ULS surgery, and to perioperative BPMT or usual care. BPMT involved pelvic floor muscle exercise training and behavioral strategies to reduce urinary and colorectal symptoms.

A “successful” surgical outcome was defined as the absence of:

- Protrusion of more than one-third of the vaginal apex into the vaginal canal
- Descent of the anterior or posterior vaginal wall beyond the hymen
- Bothersome vaginal bulge symptoms
- Surgical or pessary retreatment for prolapse

Success or failure of the BPMT intervention was determined by patients’ self-reported urinary and prolapse symptoms, and by continuing anatomic failure or retreatment for prolapse.

No Difference in Surgical Outcomes

The OPTIMAL trial found that, in the 84.5 percent of participants who underwent follow-up evaluation at two years, the proportion of patients with successful outcomes was not statistically significantly different between the two surgical procedures (ULS 59.2 percent versus 60.5 percent for SSLF).

Women in the two groups had comparable proportions of severe adverse events during the two-year postoperative evaluation period (ULS 16.5 percent versus 16.7 percent for SSLF). The most common perioperative event was bladder perforation associated with placement of tension-free vaginal tape for the retropubic midurethral sling. Less than 5 percent of the adverse events were directly related to the prolapse surgery.

BPMT patients fared the same as those who got the usual perioperative care in terms of incontinence measures at six months and prolapse symptom scores and anatomic criteria at 24 months.

No Widespread Behavioral Therapy Role at Time of Prolapse Surgery

The OPTIMAL trial results do not support routine recommendation of perioperative BPMT for women undergoing surgery for vaginal prolapse and stress urinary incontinence. However, existing evidence supports individualized behavioral or physical incontinence therapy for women who are experiencing new or unresolved pelvic floor symptoms.

OPTIMAL’s findings regarding the comparable efficacy and safety of ULS and SSLF are beneficial for preoperative decision-making, particularly in evaluating a patient’s preference for anatomic and subjective outcomes, as well as the likelihood and range of adverse events.

Individual patient characteristics will continue to dictate some variability in the choice of surgical repair technique for vaginal prolapse. But the OPTIMAL results provide a benchmark to assess other vaginal procedures, including those using synthetic or biologic mesh.

Dr. Barber, the OPTIMAL study’s lead author, is Vice Chairman, Clinical Research, at Cleveland Clinic’s Ob/Gyn & Women’s Health Institute. He can be reached at 216.445.0439 or barberm2@ccf.org.
Resources for Physicians

**Physician Directory.** View our staff online at clevelandclinic.org/staff.

**Same-Day Appointments.** Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

**Track Your Patients’ Care Online.** Establish a secure online DrConnect account for real-time information about your patients' treatment at Cleveland Clinic at clevelandclinic.org/drconnect.

**Critical Care Transport Worldwide.** To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467. Learn more at clevelandclinic.org/criticalcaretransport.

**CME Opportunities: Live and Online.** Visit ccfmce.org to learn about the Cleveland Clinic Center for Continuing Education's convenient, complimentary learning opportunities.

**Outcomes Data.** View Outcomes books at clevelandclinic.org/outcomes.

**Clinical Trials.** We offer thousands of clinical trials for qualifying patients. Visit clevelandclinic.org/clinicaltrials.

**Executive Education.** Learn about our Executive Visitors' Program and two-week Samson Global Leadership Academy immersion program at clevelandclinic.org/executiveeducation.

**Consult QD Blog for Physicians.** Discover the latest research insights, innovations, treatment trends and more. Visit clevelandclinic.org/ConsultQD.

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a non-profit academic medical center with a main campus, eight community hospitals, more than 75 northern Ohio outpatient locations (including 16 full-service family health 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 2014, Cleveland Clinic was ranked one of America’s top four hospitals in U.S. News & World Report’s annual “America’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 20th consecutive year) and urologic care.

24/7 Referrals

**Referring Physician Hotline**

855.REFER.123 (855.733.3712)
clevelandclinic.org/refer123

Live help connecting with our specialists, scheduling and confirming appointments, and resolving service-related issues.

**Hospital Transfers**

800.553.5056

Stay Connected to Cleveland Clinic on …

Download our NEW Physician Referral App today!

Contacting us is now easier than ever before.

With our free Physician Referral App, you can view all of our specialists and get in touch immediately with one click of your iPhone®, iPad®, or Android™ phone or tablet.

DOWNLOAD TODAY at the App Store or Google Play.