Summer 2015

Cleveland Clinic

Ob/Gyn & Women's Health
Research Perspectives

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

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By Toby Cosgrove, MD,
CEO and President of Cleveland Clinic

Great things happen when a medical center puts patients first. For details or to order a copy of this book, visit **clevelandclinic.org/ClevelandClinicWay**.

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Dear Colleagues and Friends:

In this edition of *Ob/Gyn & Women's Health Research Perspectives*, we are excited to introduce Dr. Miriam Cremer, the new Director of Global Health Research for our institute. You'll learn about her important work in Central and South America, where she is spearheading practical initiatives aimed at eradicating cervical cancer in underserved communities.

We also feature cutting-edge translational research on endometriosis, made possible by collaboration between academic medical centers, Cleveland Clinic and the University of Kansas (UK). We have been pleased to work with Warren B. Nothnick, PhD, at UK to elucidate the potential role of miRNA-451 in the pathogenesis of endometriosis.

We also showcase our continued efforts to develop risk calculators that allow patients and physicians to share decision-making about treatment, a key component of patient-centered care. Eric Jelovsek, MD, MMEd, explains the NICHD Pelvic Floor Disorders Network study behind the new, easy-to-use online tool for calculating risks of de novo stress urinary incontinence after pelvic organ prolapse surgery.

The importance of shared decision-making is echoed in our cover feature from Ruth Farrell, MD, MA, an expert on obstetrics and bioethics. Her ongoing research addresses lingering ethical concerns about appropriate counseling, communication and informed consent for noninvasive prenatal testing after its rapid introduction into prenatal care.

We hope you enjoy reading about the exciting research underway in Cleveland Clinic's Ob/Gyn & Women's Health Institute. Please contact us with your questions and suggestions. We welcome those interactions as well as the possibility of future collaboration.

Sincerely,

Tommaso 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

Striving to Eradicate Cervical Cancer in Underserved Countries

By Miriam Cremer, MD, MPH

Cervical cancer prevention strategies in high-resource settings are models of success. In the past 50 years, the United States and other developed nations have seen more than a 75 percent reduction in their cervical cancer rates.

Yet cervical cancer remains the third most-diagnosed female cancer worldwide, and nearly 90 percent of new cervical cancer cases are diagnosed in poor countries.

Two large research projects at Basic Health International (BHI), a nonprofit organization I founded to eradicate cervical cancer, and Cleveland Clinic seek to combat this disparity.

A low-cost screening test

The discovery that virtually all cervical cancers result from persistent cervical infections by specific HPV DNA genotypes has revolutionized prevention strategies by directly targeting the causal agent.

In 2012, BHI launched the Cervical cAncer Prevention in El Salvador (CAPE) program in partnership with the Salvadoran Ministry of Health. It is the first program of its kind to utilize a low-cost HPV DNA test (careHPV®) in a public-sector screening program.

This device, adapted from the electrically powered CryoPen, is easily transported. (Courtesy of CryoPen, Inc.)

The CAPE project will screen 30,000 women for HPV by the end of 2015 and generate data on the most effective methods of integrating HPV testing into a national screening program.

Nested within the CAPE study are multiple projects focused on increasing access and patient acceptance of new screening and treatment methods. By successfully integrating a cost-effective and comprehensive cervical cancer screening and treatment program in El Salvador, the CAPE project can serve as a paradigm to be replicated in other resource-poor countries worldwide.

Testing a portable tool

The second project, CryoPen®: An Innovative Treatment for Cervical Precancer in Low-Resource Settings, is supported by a $4 million grant from the National Institutes of Health and the National Cancer Institute. The project involves developing and testing a practical, low-cost cervical cancer treatment tool in Peru and Colombia.

The project's goal was to develop a cryotherapy system that does not rely on gas-based cryogen for testing in low- and middle-income countries.

Gas-based cryotherapy systems are limited by their expense and the need to continually refill tanks. Furthermore, they are bulky and difficult to transport. Our device, adapted from the electrically powered tabletop CryoPen, is inexpensive and easily transported. Specifically designed to overcome barriers to use of gas-based cryotherapy in underserved countries, it will be resilient under extreme conditions, compatible with unstable electrical systems and operable from a car battery when traditional electrical sources are unavailable.

The CAPE program is the first to use the low-cost careHPV test for public-sector cervical cancer screening. (Courtesy of Basic Health International)

Early data encouraging

Preliminary data already show that tip temperatures for a prototype of the adapted device are equivalent to those of the original CryoPen and of the more standard carbon dioxide-based cryotherapy.

Our study will investigate how effectively the adapted CryoPen can treat cervical intraepithelial neoplasia grade 2 and higher (CIN2+).

The study's results have the potential to create treatment paradigm alternatives that could be used in low- and middle-income countries around the world, extending treatment to the most vulnerable, underserved and unscreened populations. ■

Dr. Cremer, Director of Global Health Research for the Ob/Gyn & Women's Health Institute and President and Founder of Basic Health International, can be reached at 216.312.0618 or at cremerm@ccf.org.

What Roles Do MicroRNA-451 and Macrophage Migration Inhibitory Factor Play in Endometriosis?

By Warren B. Nothnick, PhD, HCLD, and Tommaso Falcone, MD, FRCSC, FACOG

Endometriosis is a chronic, recurrent disease affecting as many as 1 in 10 of all women of reproductive age. Anti-hormonal treatment is often unacceptable, and surgery is often required to treat pelvic pain, dysmenorrhea and infertility.

The lack of adequate treatment stems largely from our poor understanding of factors that lead to the establishment and survival of endometrial stromal and glandular tissue in ectopic locations.

Debate persists over the mechanisms by which endometriosis develops, but reverse menstruation of viable endometrial tissue into the peritoneal cavity has the greatest support. One of this theory's shortcomings is that almost all women of reproductive age exhibit some degree of retrograde menstruation, strongly suggesting that additional unidentified factors contribute to disease development and progression.

Potential microRNA role

MicroRNAs (miRNAs) are small, non-coding regulatory RNAs that regulate gene expression after transcription. The expanding field of research on miRNA strongly supports its ability to regulate multiple factors involved in cellular adhesion, proliferation and survival — cellular events essential for endometriotic lesion establishment and survival.

MicroRNA-451 (miR-451) demonstrates misexpression in endometriotic lesion tissue and may be of considerable clinical interest. In experimental disease models, miR-451 regulates several transcripts whose proteins play pivotal roles in endometriotic lesion survival; macrophage migration inhibitory factor (MIF) may be among the most important.

Studying tissue retrospectively

To assess the expression and possible function of miR-451 in endometriosis, we conducted a retrospective study of 30 women undergoing surgical treatment for endometriosis.[1] Our analysis of matched eutopic (N = 30) and endometriotic (N = 43) lesion tissues from the subjects included:

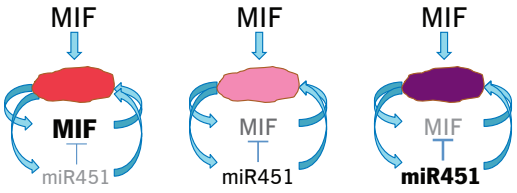
- Quantitative real-time polymerase chain reaction (qRT-PCR) to assess expression levels of miR-451 as well as those of MIF, CCNE and PTEN mRNA
- Western blot analysis of MIF protein levels
- 3'UTR reporter assays and Western blot analysis to assess the functional ability of miR-451 to regulate MIF translation in vitro
- In vitro cell survival assays to confirm the ability of miR-451 to regulate epithelial cell proliferation

Shedding light on miR-451 function

Both MIF mRNA and protein were significantly ($P < 0.05$) decreased in endometriotic lesions as compared to eutopic endometrium. This finding was associated with a significant ($P < 0.05$) increase in miR-451 expression. Transfection of hES cells with luciferase reporter constructs for MIF revealed that miR-451 specifically bound to the 3'UTR to regulate expression.

Further, forced expression of miR-451 induced significant ($P < 0.05$) downregulation of both MIF mRNA and protein in epithelial cells, a finding associated with a significant ($P < 0.05$) reduction in cell survival. MIF inhibition using a specific antagonist verified that reduction of MIF contributes to epithelial cell survival.

Lastly, elevated miR-451 and reduced MIF were associated with reduced cell proliferation; *CCNE1* expression was reduced and *PTEN* was elevated in endometriotic lesion tissue.



Forced expression of miR-451-induced significant downregulation of both MIF mRNA and protein in epithelial cells, which was associated with a significant reduction in cell survival.

Thus, we propose that in the pathogenesis of endometriosis, elevated miR-451 may function to regulate MIF expression in an attempt to curtail endometriotic lesion tissue/cell survival. In contrast, lesions that express low levels of miR-451 and elevated MIF may be more apt to survive.

Ongoing research

The potential of a switch from low to elevated expression of miR-451 and the modulation of MIF expression as a mechanism to limit survival over the life span of endometriotic lesions is being explored. ■

Dr. Nothnick is Professor of Molecular & Integrative Physiology and Scientific Advisor for Laboratory Animal Resources at the University of Kansas Medical Center.

Dr. Falcone is Professor and Chair of Cleveland Clinic's Ob/Gyn & Women's Health Institute and may be reached at 216.444.1758 or falcont@ccf.org.

1. Graham A, Falcone T, Nothnick WB. The expression of microRNA-451 in human endometriotic lesions is inversely related to that of macrophage migration inhibitory factor (MIF) and regulates MIF expression and modulation of epithelial cell survival. *Hum Reprod* 2015;30(3):642-652.

Noninvasive Prenatal Testing: Exploring Informed Consent

By Ruth M. Farrell, MD, MA

The rapid uptake of noninvasive prenatal testing (NIPT) in prenatal care presents distinct challenges to obstetric providers to offer pregnant women the information they need to make informed decisions about this test. In a recent study, we identified best practices regarding the implementation and presentation of NIPT as a testing option.

NIPT, one of the newest aneuploidy testing options, analyzes cell-free fetal DNA in maternal blood. It is more sensitive and specific for trisomy 21, 18 and 13 than conventional serum analyte screens; provides information about sex chromosome aneuploidies; and is beginning to be used to screen for fetal genomic microdeletion syndromes.

Informed consent remains an essential component of NIPT. Yet the pace with which NIPT has been integrated into prenatal care has offered little opportunity for the design and implementation of effective, evidence-based strategies to support a patient-centered informed consent process that addresses the challenges of the practice of medicine. Such strategies are critical for providers when they discuss NIPT as an option with pregnant patients.

Our study was designed to develop these strategies. We used qualitative methods to analyze self-reported needs for information about NIPT and identified the decision-making resources needed to structure an effective, patient-centered consent process. This data allowed us to explore a variety of perspectives and personal experiences in participants' own words, providing a context in which to understand the patient-provider dynamics and provide patient-centered care.

Study design

The study included 137 women who were either pregnant or had delivered in the past three months. Over 18 months, a series of focus groups and in-depth interviews used a series of specific questions to identify participants' perspectives on counseling, decision-making and the informed consent process.

Participants were asked to identify the information and resources needed to make an informed choice about NIPT, to speak about their experiences with the NIPT process, and to give their recommendations on designing and implementing clinical tools and strategies.

Digital focus group recordings were transcribed verbatim and verified for accuracy by the research team. Data analysis — an iterative, progressive process of data immersion, coding, memoing and theme identification — was inductive and consistent with grounded theory.

Key factors in informed consent

Participants favored NIPT over conventional screens because of its accuracy, early timing, ease of testing and ability to determine fetal sex. Yet such advantages did not simplify decision-making, minimize the importance of the informed consent process, or reduce the amount of support sought from providers when making informed choices about their testing options.

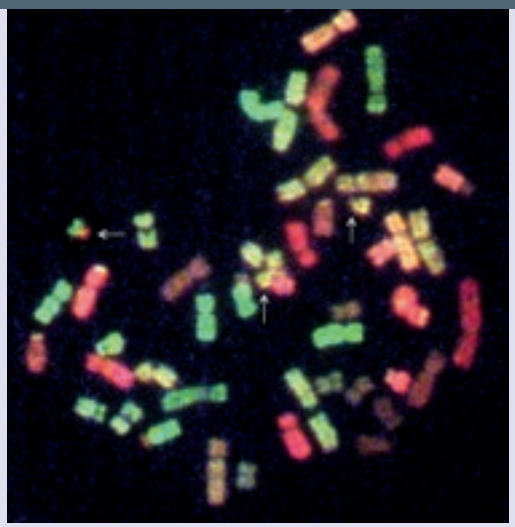
Participants identified several factors required for effective counseling:

- Information comparing NIPT with other screens, including how detection rates differ for different genetic conditions
- Information about the chance of a false positive and false negative result
- Ongoing decision support at all stages of screening, as NIPT's superior test characteristics failed to abate the anxiety associated with prenatal genetic testing
- A process for counseling and informed consent that would allow women to fully comprehend the benefits and limitations of NIPT, as well as the personal and ethical implications of test results

We also examined participants' knowledge and attitudes about the use of NIPT for conditions other than trisomy 21, 18 and 13. We found that participants were generally unfamiliar with sex chromosomal aneuploidies, the prevalence of such aneuploidies, and the spectrum of associated health issues.

In addition, one of NIPT's emerging applications is screening for a limited number of fetal genomic microdeletion syndromes. Yet participants were even less familiar with the concept of chromosomal microdeletions and the clinical phenotypes of associated syndromes (upon which some testing platforms are based) than they were with sex chromosomal aneuploidies.

Participants acknowledged that NIPT's growing capabilities would increase the volume of information that must be effectively communicated during the informed consent process. At the same time, they were concerned that time not be taken away from the discussion of



other critical educational components in prenatal care.

New approaches and tools

There is a critical need to offer sufficient information and resources to enable patients to make informed decisions about NIPT. However, the use of NIPT for screening for microdeletions, as well as its use among low-risk populations, will further strain the resources of obstetric providers.

Not only are new approaches to education and informed consent required, but efforts must also be coordinated among obstetricians, nurse midwives, and maternal-fetal medicine and prenatal genetic specialists.

We are currently investigating these issues in larger and more diverse populations. We are also developing and testing resources that will help both providers and pregnant patients meet the challenges associated with NIPT. ■

Dr. Farrell, a member of the Department of Obstetrics as well as the Department of Bioethics, can be reached at 440.943.2500 or at farrelr@ccf.org.

This research was supported in part by a March of Dimes Foundation grant. Collaborators include Pat Agatisa, PhD; Mary Beth Mercer, MA; Marissa Smith, CGC; Elliot Philipson, MD; Angela Leek; and Rebecca Starck, MD.

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A Randomized, Open-Label Study Comparing the Combination of Yondelis and Doxil/Caelyx with Doxil/Caelyx Monotherapy for the Treatment of Advanced-Relapsed Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer
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A Multinational, Randomized, Open-Label Phase 3 Study of MEK162 vs. Physician's Choice Chemotherapy in Patients with Recurrent or Persistent Low-Grade Serous Carcinoma of the Ovary, Fallopian Tube or Primary Peritoneum
Principal Investigator: Peter Rose, MD
Research line: 216.445.8090

INCONTINENCE

Controlling Anal Incontinence by Performing Anal Exercises with Biofeedback or Loperamide: a Randomized Placebo-Controlled Trial (CAPABLE)
Principal Investigator: Eric Jelovsek, MD
Research line: 216.445.8090

INFERTILITY

Determining the Fertility Benefit of Immediate SO+IUI After Operative Laparoscopy in Patients with Advanced Stage Endometriosis
Principal Investigator: Lisa Caronia, MD
Research line: 216.445.8090

PELVIC ORGAN PROLAPSE

A Prospective Randomized Trial Comparing Restorelle Y Mesh vs. Restorelle Dual Flat Mesh for Laparoscopic and Robotic-Assisted Laparoscopic Sacrocolpopexy
Principal Investigator: Cecile Unger, MD
Research line: 216.445.8090

A Randomized, Controlled Trial on the Effect of Local Analgesia on Postoperative Gluteal Pain in Patients Undergoing Sacrospinous Ligament Colpopexy
Principal Investigator: Cecile Unger, MD
Research line: 216.445.8090

PELVIC PAIN

Treatment of Pain Using a Non-implanted Intravaginal Electrical Stimulation Device Compared to a Vaginal Dilator in Chronic Pelvic Pain Patients
Principal Investigator: Elim Shih, MD
Research line: 216.445.8090

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Calculating the Risk of Stress Incontinence After Pelvic Organ Prolapse Surgery

By Eric Jelovsek, MD, MMEd

A significant number of women with pelvic organ prolapse develop bothersome stress urinary incontinence (SUI) after transvaginal prolapse surgery or sacrocolpopexy. A concomitant midurethral sling, Burch cystourethropexy or other procedure may be recommended as a result.

Some surgeons use preoperative prolapse reduction urinary stress tests to gauge the risk of de novo SUI, but the tests' sensitivity is just 17 to 39 percent. Other surgeons favor a "wait and see" approach.

A better means of calculating risk is needed in this era of personalized medicine, especially considering patients' expanded role in choosing treatments that impact quality of life.

An NICHD Pelvic Floor Disorders Network study[1] sought to develop and test a personalized model for better predicting the risk of de novo SUI after pelvic organ prolapse (POP) surgery.

Testing two hypotheses

We hypothesized that a prediction model using patient and testing characteristics from two large POP surgery trials could refine the risk of developing de novo SUI within 12 months of vaginal prolapse surgery. We also believed this prediction model would outperform expert predictions.

We studied data from 465 randomized participants in the Outcomes Following Vaginal Prolapse Repair and Midurethral Sling (OPUS) trial, which estimated the de novo SUI prevalence within 12 months of vaginal POP surgery with or without a tension-free vaginal tape (TVT) sling.

Refining preoperative predictors

We identified 12 possible preoperative predictors of postoperative de novo SUI: age, race, parity, body mass index, smoking, diabetes, strenuous physical activity, baseline urgency urinary incontinence symptoms, preoperative POP-Q (Pelvic Organ Prolapse Quantification System) stage, POPQ point Aa, positive preoperative prolapse reduction stress test, and a concomitant TVT.

Our primary clinical outcome was de novo SUI within 12 months of surgery, as determined by responses to Pelvic Floor Distress Inventory queries about leakage when coughing, sneezing or laughing; physically exercising (walking, running, aerobics or tennis); and lifting or bending over.

Adjusting for the 12 potential predictors through multivariable logistic regression analysis, we used step-down elimination to narrow them to seven: age, number of vaginal births, body mass index, preoperative stress test results, planned continence procedure at the time of POP surgery, urine leakage with urgency, and diabetes diagnosis.

Validating the model

We used the concordance index to assess the model's ability to discriminate between high- and low-risk patients and used bias-corrected calibration plots to test model predictions versus actual predictions.

After internal validation using 1,000 bootstrap samples, we selected the best model for external validation using Colpopexy and Urinary Reduction Efforts (CARE) trial data. CARE estimated de novo SUI rates after open abdominal sacral colpopexy, with or without Burch urethropexy.

Obtaining expert opinions

We also asked 22 experienced Pelvic Floor Disorders Network surgeons to clinically predict postoperative SUI for 32 randomly selected OPUS trial participants using the same predictors as our model.

We compared the prediction model's "area under the curve" data with experts' predictions, preoperative prolapse reduction stress tests alone and data from 322 CARE participants.

Risk calculator deemed valid

We determined that the individualized risk prediction model was valid and outperformed both subspecialist predictions and preoperative stress test results.

The online calculator's ease of use makes it a valuable tool for discussing vaginal POP surgery and concomitant continence surgery options with patients. The tool is available at clevelandclinic.org/denovoSUIcalculator. ■

Dr. Jelovsek, Associate Professor in Female Pelvic Medicine and Reconstructive Surgery and Vice Chair of Education for the Ob/Gyn & Women's Health Institute, was principal investigator for the NICHD Pelvic Floor Disorders Network study. He may be reached at 216.444.2488 or jelovsj@ccf.org.

1. Jelovsek JE, Chagin K, Brubaker L, et al. A model for predicting the risk of de novo stress urinary incontinence in women undergoing pelvic organ prolapse surgery. *Obstet Gynecol* .2014;123 (2 Pt 1):279-287

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Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,200 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 90 northern Ohio outpatient locations (including 18 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 2015, Cleveland Clinic was ranked one of America's top five hospitals 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 21st consecutive year).

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