WINTER 2016

BRIGHAM AND WOMEN'S HOSPITAL

OB/GYN ADVANCES

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Early-phase Trials at Dana-Farber/Brigham and Women's Cancer Center Explore Novel Combinations for Ovarian Cancer

Building on recent discoveries at Dana-Farber/Brigham and Women's Cancer Center using a variety of inhibitor combinations, researchers in the Susan F. Smith Center for Women's Cancers are leading new early-phase trials for patients with ovarian cancer.

"We are looking at new targeted approaches for patients with ovarian cancer, using biomarkers and other key information to identify specific patient populations that are most likely to respond to certain treatments," said Ursula Matulonis, MD, Director of the Center's Gynecologic Oncology Program. "Given the genetic complexity of the most common type of ovarian cancer, serous cancer, our group thinks that combination therapies as a strategy are very promising."

Medical oncologist Joyce Liu, MD, MPH, and Ursula Matulonis, MD, Director of the Gynecologic Oncology Program at Dana-Farber/Brigham and Women's Cancer Center, are leading new early-phase trials for patients with ovarian cancer.

Findings in PARP Combination Studies

At the 2015 American Association for Cancer Research (AACR) Annual Meeting, Dr. Matulonis presented final results of a Phase I study of the combination of the poly ADP-ribose polymerase (PARP) inhibitor olaparib and the phosphatidylinositol-3-kinase (PI3K) inhibitor BKM120 in patients with high-grade serous ovarian cancer, as well as triple-negative breast cancer. The study demonstrated the safety of the combination and showed efficacy in both BRCA-mutant and BRCA-wildtype cancers.

A previous multi-center phase II trial, Combination Cediranib and Olaparib versus Olaparib Alone for Women with Recurrent Platinum-sensitive Ovarian Cancer (*Lancet Oncol.* 2014 Oct;15(11):1207-14), led by the overall Principal Investigator Joyce Liu, MD, MPH, and co-PI Dr. Matulonis compared the combination of olaparib and cediranib, an anti-angiogenic agent, with olaparib alone in patients with ovarian cancer. The trial not only showed that the combination was more active than olaparib alone but that activity was observed in both BRCA-mutation carriers and BRCA non-carrier participants.

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Team-based Strategies and Web-based Tools Benefit Complex Management of Diabetes in Pregnancy

Providing expert care for patients with pre-existing diabetes and gestational diabetes mellitus (GDM), endocrinologists and maternal-fetal medicine specialists in the Diabetes in Pregnancy Program at Brigham and Women's Hospital (BWH) are utilizing innovative strategies to manage diabetes in pregnancy.

"Many of our patients have highly complex needs with vascular and other complications from diabetes and may be on the verge of needing dialysis when they come to us," said Chloe A. Zera, MD, MPH, a maternal-fetal medicine specialist in the Program. "In order to see these patients safely through pregnancy and improve their health and their families' health for the long term, we deliver seamless outpatient and inpatient care and delivery and postpartum follow up."

Broad Spectrum of Advanced Care

Patients are evaluated and treated in a multidisciplinary clinic using a team-based model with endocrinologists, maternal-fetal medicine specialists, nurse practitioners, social workers, and nutritionists collaborating in the care of each patient in a single visit. The team employs an evidence-based approach to control diabetes while managing changes during pregnancy. Progressive approaches to medication management include expertise in insulin pump and continuous glucose monitoring, use of U-500 insulin, and oral agents when appropriate. To optimize a woman's health prior to pregnancy, Emma Morton-Eggleston, MD, an endocrinologist in the Program, and Dr. Zera frequently counsel patients with Type 1 and Type 2 diabetes prior to conception.

"As more women develop Type 2 diabetes during their childbearing years and women with Type 1 diabetes plan pregnancies, we are facing an increasing number of challenging cases of pre-existing diabetes during pregnancy and growing concerns about both adverse outcomes in the short term and childhood metabolic outcomes, including childhood obesity," said Dr. Morton-Eggleston. "The normal physiologic changes of pregnancy can make it very difficult to control glycemia and manage complications throughout pregnancy, even for patients who have previously had good control. It is critical to provide care with an integrated approach that provides advanced clinical expertise with a supportive approach that maximizes maternal and fetal outcomes while allowing women and their families to feel engaged in their care."

Endocrinologist Emma B. Morton Eggleston, MD, MPH (center), and maternal-fetal medicine specialist Chloe Zera, MD, MPH (right), along with their colleague endocrinologist Ellen W. Seely, MD, director of clinical research, lead the Diabetes and Pregnancy Program at BWH.

Improving Long-term Outcomes Following Gestational Diabetes

Ellen W. Seely, MD, Director of Clinical Research in the Division of Endocrinology, Diabetes and Hypertension at BWH, and her team, including Dr. Zera, developed Balance after Baby, a web-based lifestyle intervention funded by the Centers for Disease Control and Prevention to promote weight loss after pregnancy by educating women on eating healthfully and increasing their physical activity. In a study published in 2014 (*Obstet Gynecol.* 2014 Sep;124(3):563-70.), the team found that women who followed the online program reached their pre-pregnancy weight at one year after delivery, compared with weight gain in the control group of women with gestational diabetes who received standard care after delivery.

"We know that up to 60 percent of women who have gestational diabetes go on to develop Type 2 diabetes and that this risk is particularly high during the decade after birth," said Dr. Seely. "We were able to demonstrate the feasibility and efficacy of a lifestyle modification program in decreasing postpartum weight retention in the first postpartum year for women with recent GDM."

Access to Specialized Services

At Brigham and Women's Hospital, our OB/GYN staff are available for timely consultations and will work with you to develop treatment plans for your patients. Our Physician Liaison Tom Anderson can provide direct assistance with patient referrals and consultations. Tom can be reached at (617) 582-4760 or tanderson0@partners.org.

Ongoing Research

The team is engaged in a wide range of ongoing research related to diabetes in pregnancy. A current study using the Balance after Baby program is following women for two years after pregnancy to see if the weight loss is sustained and whether glucose levels are controlled during this time. As a founding member of the Diabetes in Pregnancy Study Group, the team is planning to launch a cohort study of psychosocial predictors of diabetes-related pregnancy outcomes in 2016. Dr. Zera and Dr. Morton-Eggleston are collaborating on a program to improve the post-delivery transition to primary care physicians with an emphasis on ongoing screening and diabetes prevention strategies for women. Dr. Zera is developing a pragmatic trial of yoga to improve measures of stress and quality of life for women with diabetes during pregnancy.

"We are looking at the larger picture with the goal to promote health throughout the woman's lifespan, not just during pregnancy," said Dr. Zera.

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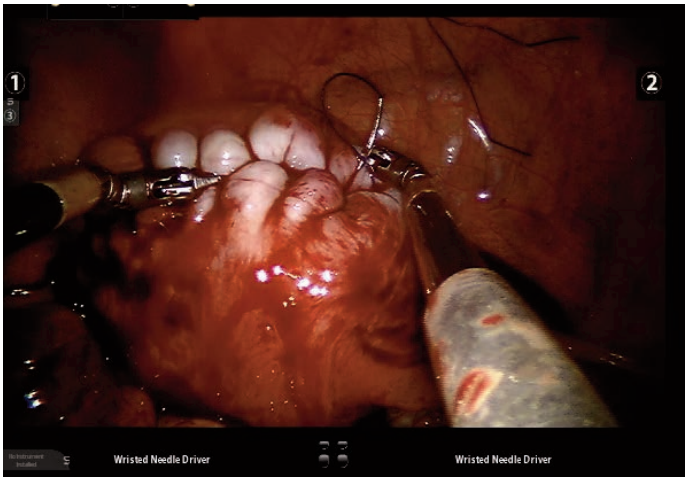
World's First Robotic Single-Site Myomectomy Developed by BWH Surgeons

A team led by Antonio R. Gargiulo, MD, Medical Director for the Center for Robotic Surgery at Brigham and Women's Hospital (BWH), has been the first to publish and describe a technique that employs dedicated single-site robotic technology to perform a myomectomy through a single incision in the umbilicus (*Fertil Steril.* 2015 Aug 20. pii: S0015-0282(15)01671-4.).

Aside from the evident cosmetic advantages over conventional multi-port myomectomy, the ability to perform the operation through a single 2.5 cm long entry (hidden within the umbilicus in most patients) offers a range of potential advantages deriving from the avoidance of several additional surgical entry points, including:

- Less postoperative pain;
- Decreased risk of injury to the abdominal wall, bowel, and blood vessels;
- Reduced risk of future post-surgical hernia formation.

Select patients with one or two uterine fibroids under eight centimeters and a total tumor load of less than 10 fibroids are considered candidates for robotic single-site myomectomy. Dr. Gargiulo and his team began offering single-site robotic surgery in 2013 and have completed more than 25 robotic single-site myomectomy cases to date since new technology allowing this procedure has become available in 2014. In this selected group of patients, the team has observed no complications and no conversions to multi-port surgery or open surgery to date. Most patients for whom a single-site myomectomy is not recommended can still undergo robotic myomectomy with other cosmetic or standard port-placements, depending on the size and number of their fibroids.



"This unique ultra-minimally-invasive surgical approach is highly reproducible and successful because it was developed by a surgical team with an enormous cumulative experience in robotic surgery," said Dr. Gargiulo. "We continue to build on our unique knowledge of these tools, based on a decade of intense experience in the field, to introduce new approaches and refine existing techniques."

To see a video tutorial of this procedure, please visit **brighamandwomens.org/singlesitemyomectomy.**

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Early-phase Trials at Dana-Farber/Brigham and Women's Cancer Center Explore Novel Combinations for Ovarian Cancer... continued from front cover

New Early-phase Studies

The team is currently expanding its Phase I and Phase II trials using PARP inhibitors, immunotherapies, antibody drug conjugates, and other agents, to include new combinations and patient populations. Current and upcoming studies include:

- Phase I/II trial of niraparib, a PARP inhibitor, plus pembrolizumab, an anti-PD-1 immunotherapy agent, in patients with ovarian and breast cancers. *Site Principal Investigator: Panagiotis A. Konstantinopoulos, MD, PhD;*
- Phase I dose-expansion study of BYL719 or BKM120, both PI3K inhibitors, with olaparib in patients with high-grade serous ovarian cancer and recurrent triple negative breast cancer. *National Principal Investigator: Ursula Matulonis, MD*;
- Phase I study of ricolinostat, an oral HDAC6 inhibitor, together with weekly paclitaxel in recurrent platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer. *Site Principal Investigator: Joyce Liu, MD, MPH;*

(For information on these trials, please contact Christin Whalen, RN, at cwhalen@partners.org or (617) 582-7738)

"These early-phase studies enable us the ability to offer additional options for patients with advanced ovarian cancer and evaluate the effects of new drug types and combinations in extending survival," said Dr. Liu.

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BWH RESEARCH HIGHLIGHT:

Comprehensive Examination of Antidepressant Use in Pregnancy Results in New Finding about Pulmonary Hypertension Risk in Newborns

Researchers at Brigham and Women's Hospital (BWH), led by Krista F. Huybrechts, PhD, MS, an epidemiologist in the Division of Pharmacoepidemiology and Pharmacoeconomics, have published a large population-based study examining the safety of antidepressant use and its impact on risk for pulmonary hypertension of the newborn.

Published in the *Journal of the American Medical Association* (*JAMA*. 2015 Jun 2;313(21):2142-51),the team's study of antidepressant use late in pregnancy and the risk for pulmonary hypertension of the newborn (PPHN) included 3,789,330 pregnant women enrolled in Medicaid from two months or less after the date of their last menstrual period through at least one month after delivery. Among these women, 128,950 (3.4 percent) filled at least one prescription for an antidepressant late in pregnancy (102,179 used an SSRI, and 26,771 used a non-SSRI antidepressant). The reference group consisted of women without exposure to antidepressants at any time during pregnancy. After restricting the cohort to women with depression and adjusting for confounding variables, the adjusted odds ratio was 1.10 (95 percent CI, 0.94-1.29) for SSRIs and 1.02 (0.77-1.35) for non-SSRIs. Upon restriction of the outcome to primary PPHN, the adjusted odds ratio for SSRIs was 1.28 (1.01-1.64) for SSRIs and 1.14 (0.74-1.74) for non-SSRIs.

"Although we cannot entirely exclude the possibility that there might be an increased risk of PPHN associated with maternal use of SSRIs late in pregnancy, the absolute risk is small and the risk increase, if present, appears much more modest than suggested in previous studies," said Dr. Huybrechts.

At BWH, experts in maternal-fetal medicine and women's mental health collaborate to deliver expert care for women with psychiatric conditions before, during, and after pregnancy. "Our goal is to help our patients make informed choices about the use of antidepressants and other psychiatric medications during pregnancy alongside non-medication treatment options," said Leena P. Mittal, MD, Director of the Reproductive Psychiatry Consultation Service within the Department of Psychiatry at BWH. "We rely on large-scale studies such as this to provide valuable data and guidance for patients trying to make choices that will optimize their mental health and the wellbeing of their growing families."