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UPDATES IN GYNECOLOGY

DEPARTMENT OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE SCIENCES

Inside This Edition

Message from the Chairman

Dear Colleagues,

I am pleased to share with you some of the latest news, research, and clinical advances from our Department of Obstetrics, Gynecology, and Reproductive Sciences.

The fertility preservation work of **Kyle Orwig, PhD**, and colleagues continues to advance the field and revolutionize what is and may be possible with preserving and restoring fertility for young cancer patients and others.

We are reshaping clinical practice through several new endeavors: A family planning initiative that is expanding access to contraceptives for women, and the growth and success of our telemedicine program for maternal-fetal medicine.

Featured clinical research from faculty in this issue discusses new clinical trials for ovarian cancer with the immunotherapy agent rintatolimod; findings related to maternal weight gain and twins; and pelvic organ prolapse surgery.

Finally, I am pleased to share that **Pamela Ann Moalli, MD, PhD**, has been promoted to be the new director of our urogynecology division, while **Halina Zyczynski, MD**, was appointed as medical director of Magee-Womens Specialty Services at UPMC Hamot in Erie, Pennsylvania.

I welcome the opportunity to hear from our colleagues around the nation and discuss opportunities for collaboration.

Robert P. Edwards, MD
Chair, Department of Obstetrics, Gynecology, and Reproductive Sciences
Co-Director, Gynecologic Oncology Research, UPMC Magee-Womens Hospital

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Fertility Preservation Program in Pittsburgh: Scientific Milestones and Technological Advances Closing In on the Clinic

Kyle Orwig, PhD, is a professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences with secondary appointments in micro-biology and molecular genetics, and developmental biology. He is primary investigator of the Orwig Laboratory, director of research in reproductive endocrinology and infertility, and director of the Fertility Preservation Program in Pittsburgh of UPMC (**FertilityPreservationPittsburgh.org**).

As Director of the Orwig Laboratory, Dr. Orwig and his colleagues are investigating numerous lines of research crucial to developing more complete understandings of spermatogenesis, oogenesis, and various conditions that lead to infertility in men and women. Dr. Orwig and his laboratory have ongoing investigations into the molecular mechanisms that control spermatogonial stem cells and their basic biology; testicular and germline development; stem cell therapies to treat forms of male infertility; and a number of IRB-approved experimental protocols testing new clinical technologies for fertility preservation and restoration.

In collaboration with the Division of Reproductive Endocrinology and Infertility, the Fertility Preservation Program in Pittsburgh of UPMC provides the most comprehensive menu of fertility preservation options available anywhere in the country, including both standard of care and experimental options for women, men, girls, and boys. The program has provided national and international leadership by offering experimental testicular and ovarian tissue freezing for children — specifically, those children with a clinical cancer diagnosis whose chemotherapy or radiation treatments put them at significant risk for future infertility as a consequence of gonadotoxic therapies. Children are not able to produce mature eggs or sperm, so ovarian and testicular tissue freezing is the only fertility preservation option available to them.

At present, there are few options to use ovarian tissues or testicular tissues obtained from children to produce mature eggs or sperm that can be used for reproductive purposes. The most progress has been made with ovarian tissues, which can be transplanted back into the patient and ovulate eggs into the uterus in the usual way. About 150 babies have been produced from transplanted ovarian tissues, including two from adult survivors of childhood cancers. No human babies have been produced from cryopreserved testicular tissues yet, but Dr. Orwig's team has made pioneering strides on this front in nonhuman primates, with groundbreaking results being published last year in the journal *Science*.

A Birth From Cryopreserved and Implanted Testicular Tissue

In a major first, Dr. Orwig and colleagues at the University of Pittsburgh School of Medicine and the Magee-Womens Research Institute (MWRI) reported in March, 2019, in the journal *Science*[1] that in a nonhuman primate model immature testicular tissue can be cryopreserved and later used to restore fertility to the same animal.

This advance marks a milestone in the development of next-generation assisted reproduction therapies and offers hope for fertility preservation in prepubertal boys who are about to undergo cancer treatments.

"This advance is an important step toward offering young cancer patients around the world a chance at having a family in the future," says Dr. Orwig.

In the current study, Dr. Orwig and his team developed a non-human primate model of cancer survivorship. Prior to treating with chemotherapy, the researchers removed one testis from prepubertal rhesus macaques and cryopreserved the immature testicular tissue. As the animals approached puberty, the other testis was removed. On the same day, they transplanted pieces of the freshly collected tissue as well as pieces of tissue that were cryopreserved months earlier under the skin of the same animal. As the animals entered puberty, their testosterone levels increased, causing the grafted tissue to mature and produce sperm.

Eight to 12 months later, after the animals entered puberty, the researchers removed the grafts and found large numbers of sperm to be present. They sent the sperm to their collaborators at the Oregon National Primate Research Center at Oregon Health & Science University who were able to generate viable embryos, which were then transferred to recipient females.

In April 2018, one of the females gave birth to a healthy female baby, which Orwig named "Grady" — a portmanteau of "graft-derived" and "baby."

"With Grady's birth, we were able to show proof-of-principle that we can cryopreserve prepubertal testicular tissue and later use it to restore fertility as an adult," says first author Adetunji Fayomi, PhD, a former graduate student in Dr. Orwig's laboratory and a postdoctoral scholar at the University of Pittsburgh.

Dr. Orwig notes that in comparison to previous work published by others, they used a different cryopreservation protocol and grafted larger pieces of testicular tissue, which may have contributed to the success of the current effort.

"The reason that we did these studies in a nonhuman primate is because we thought that this was the last step on the road to translating to the clinic," says Dr. Orwig. "Having produced a live-born and healthy baby, we feel that this is a technology that is ready to be tested in the clinic."

In preparation for clinical translation, Dr. Orwig established a fertility preservation program in 2010 at UPMC Magee-Womens Hospital. The program offers pediatric cancer patients the option of cryopreserving testicular or ovarian tissue before starting cancer treatments. Since then, it has expanded through collaborations with centers around the world. Orwig hopes that when these patients grow up and want families of their own, they will have that option.

Testicular Tissue Cryopreservation: Documenting Eight Years of Remarkable Success

In May, 2019, Dr. Orwig and colleagues published findings on their testicular tissue cryopreservation protocol and multicenter network in the journal *Human Reproduction.* The paper details the first eight years of their experience in harvesting and preserving testicular tissue from prepubertal boys with a cancer diagnosis who needed gonadotoxic chemotherapy for their disease that would likely render them infertile for the remainder of their lives. The goal in preserving the tissues is to someday restore the person's fertility at a time when they are ready to have children and at a time when the technologies exist in the clinic in order to make that a reality.

Ideally, children will have tissues biopsied and preserved prior to starting chemotherapy. However, one of the findings in the paper suggests that even children who have started chemotherapy and are in the early stages of treatment can still have tissues preserved that contain viable spermatogonia.

"Pittsburgh serves as the hub of the network and provides centralized processing of testicular or ovarian tissues. Thus, patients can have surgery to collect testicular tissues or ovarian tissues in the institutions where they are being treated for their cancer. Tissues are express-shipped to Pittsburgh where the tissue is processed and cryopreserved. We have 10 other sites in the network in the United States and in Israel. We have cryopreserved tissues for more than 250 individuals, many of whom are from outside the United States," says Dr. Orwig.

Dr. Orwig goes on to explain that this network approach is the ideal model for children's hospitals, most of which have the expertise to treat cancer patients and perform surgery but not the infrastructure or expertise to process reproductive tissues. The Pittsburgh center has the infrastructure and expertise to provide these services. This model allows patients to access experimental fertility preservation services without having to travel to Pittsburgh for their surgery.

Work is progressing in animal models as reported in a recent paper in *Science.* In the next several years, it is likely that proof-of-concept studies in human adults will be completed prior to beginning the work necessary to implant the preserved tissues of children and, with hope, generate viable sperm or eggs and the restoration of fertility.

New Research and Fertility Preservation Work With Transgender Patients — Adults and Children

For the last five years, Dr. Orwig and colleagues have been at work on fertility preservation studies with transgender adults, and very recently have begun to develop protocols for studies with transgender children.

"This work began with one patient who was referred to our clinic, a male to female transgender patient. She had the desire to bank a semen sample for potential use in the future. The issue at the time was this individual was in the middle of their transition, and stopping hormone therapy in order to get a sperm sample is highly problematic for a number of issues, one of which is the psychological aspects," says Dr. Orwig.

While the experience with this one patient ultimately ended up with her coming off the hormone therapy for five months in order to be able to generate sperm, the case sparked many questions in Dr. Orwig's mind about fertility preservation for transgender individuals.

"I began having conversations with colleagues in the field who are experts in transgender medicine. I wanted to know are their treatments reversible? Is there a point after which they are not reversible? Can sperm be collected while a person is still undergoing treatment, and if so, is the sperm functional? What is the psychological impact of having to stop transgender treatments? Nobody knew the answer to these questions, and as a researcher, that is my cue to get started working out answers to these questions," says Dr. Orwig.

From that first patient, Dr. Orwig and colleagues learned quite a bit. They learned that the treatments are reversible and for how long, approximately, they needed to be stopped in order for the individual to produce sperm again. They also learned that the psychological impact of having to stop the transgender transition treatments for this one individual was quite difficult.

Subsequently, work was begun in the laboratory to develop transgender male and transgender female mouse models to begin the process of understanding the basic science at play, and also to ask the question of whether healthy babies can be born from eggs and sperm in these murine models. This work is currently ongoing.

At the same time, Dr. Orwig and colleagues have been approached by families from around the world with inquiries about preserving the testicular or ovarian tissues of young children before they start transgender treatments. The immediate answer was no because there was no IRB-approved experimental protocol in place. However, because of the interest and the desire to help these children and their families, Dr. Orwig and his team set about the process of developing a protocol. Now the program is approved to freeze ovarian tissue from transgender males and testicular tissue for transgender females.

Bringing Next-Generation Reproductive Technologies to the Clinic

While Dr. Orwig and colleagues have had remarkable success in their basic science and clinical programs, and experimental protocols for young boys and girls, that success alone is not enough. Advancing the

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Maternal Weight Gain and Twins

An old adage urges pregnant women to "eat for two." So with twins, is it "eat for three?" While that is likely bad advice, when it comes to twin pregnancies, clinicians don't have firm guidelines for ideal weight gain due to a lack of scientific study.

New research led by scientists at the University of Pittsburgh Graduate School of Public Health and the University of Pittsburgh School of Medicine Department of Obstetrics, Gynecology, and Reproductive Sciences published in October, 2019, in the journal *Obstetrics & Gynecology* is beginning to establish evidence-based guidelines for maternal weight gain while pregnant with twins. The researchers identified ranges above and below which the risk of adverse outcomes, such as preterm birth and infant death, increases.

"Twin pregnancies have high rates of complications, so it is important to identify factors that we can modify during pregnancy to lessen these risks," says lead author **Lisa Bodnar, PhD, MPH, RD**, professor in the Department of Epidemiology. "Health care providers can work with women to maintain their weight gain within a targeted range, but previously, the lack of evidence on what that optimal range was left to the women and their doctors to make educated guesses or not to discuss weight gain at all."

Over the past 40 years, the number of twins born in the United States has nearly doubled. Compared with singletons, twins are more than twice as likely to die during pregnancy, and four times as likely to die in the first year of life. And while twins make up 3.3 percent of all births, they account for more than 20 percent of preterm births. Women pregnant with twins also are more likely to experience diabetes, preeclampsia, and Caesarean deliveries.

"At the initial prenatal visit for women pregnant with twins, we review a number of obstetrical complications that are more common with twins, emphasizing that gestational weight can decrease the risk of some of these complications," says study co-author **Katherine Himes, MD, MS**, assistant professor of Obstetrics, Gynecology, and Reproductive sciences and a UPMC Magee-Womens Hospital obstetrician-gynecologist in the Division of Maternal Fetal Medicine.

"On top of all the other recommendations patients are trying to digest, many women pregnant with twins are overwhelmed when they are counseled that they have to gain 40 to 50 pounds. We really need more robust data to inform this recommendation."

The research team gathered data from Pennsylvania infant birth and death vital statistics records on 27,723 twin pregnancies from 2003 to 2013. They matched the records with the mothers' pre-pregnancy height and weight, and weight at delivery. The mothers were classified as underweight, normal weight, overweight, or obese, based on their pre-pregnancy height and weight.

From that data, the team calculated an increased risk of poor birth outcomes when weight gain was:

- Less than 31 pounds or greater than 60 pounds in underweight and normal weight women
- Less than 24 pounds or greater than 62 pounds in overweight women
- Less than 14 pounds or greater than 57 pounds in obese women

"These are starting ranges," says Dr. Bodnar, who also is affiliated with the Magee-Womens Research Institute. "We are not saying that gaining within these weight ranges is necessarily best for the health of the mother and her babies, but simply that gaining above or below them carries greater risk of poor health. Women should talk with their health care providers to determine a safe amount of weight gain for them."

The research team plans to conduct future research to further refine ideal weight gain ranges for women pregnant with single babies and twins.

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New Findings in Pelvic Organ Prolapse Surgery

According to new data from a nationwide consortium involving researchers at Magee-Womens Research Institute and patients at UPMC Magee-Womens Hospital, women had comparable clinical outcomes three years after pelvic organ prolapse surgery — regardless of whether the surgeon used mesh to suspend the uterus or removed the uterus entirely.

The results of this randomized, blinded clinical trial were published in September, 2019, in the *Journal of the American Medical Association (JAMA).*

"The findings of this study refute to a great degree the negative associations with vaginal mesh and challenge the traditional dictum that the uterus needs to be removed," says principal investigator of the Pittsburgh site **Halina Zyczynski, MD**, professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine, and medical director of Magee-Womens Specialty Services at UPMC Hamot.

Pelvic organ prolapse occurs when one or more of the pelvic organs drop from their normal position and bulge into the vagina or protrude beyond the opening of the vagina. This condition is common following childbirth and in old age, and can cause intimate discomfort and problems urinating, as well as pain. Approximately 13 percent of women in the United States will undergo a procedure for vaginal prolapse by the age of 80.

To rigorously determine how the clinical outcomes compare between surgeries involving uterine suspension with mesh versus hysterectomy, the Study of Uterine Prolapse Procedures – Randomized Trial (SUPeR) recruited 183 postmenopausal women at nine centers across the nation. Ninety-three women were randomized to mesh surgery and 90 were randomized to hysterectomy. The women were not told which procedure they would receive.

"For three years, 75 percent of the women did not know if they had a uterus or not. It shows how much they wanted to support scientific research and improve their quality of life," says Charles Nager, MD, lead author of the study and chair of obstetrics, gynecology, and reproductive sciences at UC San Diego Health. "Our team is so grateful for their cooperation. They helped us conduct a high-quality study for the future of health care."

Over the three-year study period, the mesh support surgery had a 12 percent lower failure rate than hysterectomy, and the researchers will continue to follow these patients for a total of 10 years to better understand whether one procedure is truly more effective than the other.

Additionally, a postsurgery survey found 90 percent of patients in both groups reported "much better" or "very much better" improvement. There also were no differences in patient-reported surgical or pelvic pain, and both groups reported improvements in sexual function and lower incidence of painful sex.

While this paper was being prepared, the U.S. Food and Drug Administration (FDA) halted the sale and distribution of mesh kits used for this type of surgery, citing insufficient evidence from the manufacturers to reasonably demonstrate safety and efficacy.

"At this time, we are unable to offer our patients the option of the uterine suspension procedure studied in the SUPeR trial, though we expect that the FDA will consider our study findings when they revisit their decision in the next few years," says Dr. Zyczynski. "There is no better, cleaner, higher-quality data than that which is generated by randomized clinical trials."

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Fertility Preservation Program in Pittsburgh *(Continued from Page 3)*

technologies to the clinic that can restore fertility and ultimately produce offspring is the next hurdle. While it may seem like that day is far in the future, Dr. Orwig explains that several technologies have been proven to the point where translation to the clinic is imminent.

"There are stem-cell based technologies of a highly mature level replicated in animals that we have demonstrated work in nonhuman primates — monkeys. We are excited and passionate to bring these technologies to life because we have been preserving testicular and ovarian tissues for boys and girls for almost a decade. We owe it to those patients to responsibly develop the next generation of technologies so they have a viable chance at using their preserved tissues to have children one day," says Dr. Orwig.

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Maternal Fetal Medicine Telemedicine: Seven Years of Growth and Success in Improving High-Risk Pregnancy Outcomes

The Division of Maternal Fetal Medicine at UPMC Magee-Womens Hospital conducts more than 10,000 patient consults and visits every year. Since 2011, a growing number of those consults and visits have occurred through the use of telemedicine with patients in distant areas across western Pennsylvania.

Access to a maternal-fetal medicine (MFM) specialist is crucial to achieving good outcomes and preserving and protecting the health of the mother and baby in high-risk pregnancies. Unfortunately, the number of trained MFM physicians in the United States is woefully inadequate to provide these specialized services to all patients who need them. Women who live in rural areas of the country have even less access to this specialized care, and the consequences of a lack of MFM care for high-risk pregnancies are unacceptable levels of morbidity and mortality. Geography should not be a reason that causes any patient to receive suboptimal care. Telemedicine can help to bridge the care gap. Indeed, the Division of Maternal Fetal Medicine at UPMC Magee has shown not only how it can be accomplished but also what success entails.

Building an MFM Telemedicine Program and Planning for Its Future

The structural design of the program, how it was implemented, and the health outcomes for mothers and babies for the first four complete years of the UPMC MFM telemedicine program were published in June by faculty and staff of the Division in a paper in the *American Journal of Perinatology*.[1] Analyzing program data for the years 2012 to 2015, the UPMC MFM telemedicine team shows the overall utility of the program on a systemic level, patient satisfaction scores from surveys, and clinical outcomes data from the telemedicine patient cohort (n=455) compared with in-person MFM consults conducted by the Division during the same time period (n = 6,302)

Program Design, Implementation, and Growth

The MFM telemedicine program at UPMC Magee is designed in a hub-and-spoke model. Satellite telemedicine centers are strategically positioned at UPMC community hospitals in distant geographies with UPMC Magee serving as the hub where all the consults feed back to the MFM team who conduct the visits — both inpatient and outpatient. The program began in 2011 with one telemedicine site at UPMC Horizon. During the study period covered in the paper, between 2012 and 2015, four additional telemedicine centers began operation at various points in time, resulting in five total centers active by the end

of the data reporting period. Since the end of 2015, two more sites have become operational.

"It is highly likely that we will add more centers in the future as the larger UPMC system expands into new territories and as the UPMC Magee MFM program expands its reach into new community hospitals," says **Wendy Kalocay, MBA, CMPE**, program manager of women's telemedicine and assistant administrator in the Department of Women's Health at UPMC Magee.

Obstetrical ultrasound (OB-US) is critical to the maternal-fetal medicine specialty and is a core component of the UPMC MFM telemedicine platform. An OB ultrasound physician at UPMC Magee reads all obstetrical ultrasounds for every UPMC hospital that provides obstetrical services. Regardless of where the patient is treated, their images are transmitted to UPMC Magee and examined by OB/GYN ultrasound physicians who are all board-certified maternal-fetal medicine specialists.

"All of the ultrasonographers at each UPMC hospital have been specially trained at UPMC Magee. This ensures everyone has the same qualifications and standards as the diagnosticians at UPMC Magee. During telemedicine consults, ultrasound technicians provide guidance and real-time visualization of the imaging coupled with interactive patient discussions of the results," says Ms. Kalocay.

MFM Telemedicine Goals and Objectives

- Increase access to specialists
- Reduce travel time and expense for patients
- Improve quality of care
- Eliminate unnecessary procedures and duplicate testing
- Provide timely treatment close to home
- Improve coordination of care
- Allow access to medical history by physicians

In addition to the crucial role of standardized OB-US practices built into the MFM telemedicine consults and MFM program as a whole, several other patient services have been added to the UPMC MFM telemedicine program since its inception: diabetes education, genetics testing and counseling, and preconception counseling. Tangential services for MFM patients that are not necessarily part of the current telemedicine program also have been implemented, such as a postpartum remote blood pressure monitoring program for women diagnosed with various forms of hypertension.

Key Outcomes From the First Four Years

During the first four years of the program, 455 unique patients had MFM telemedicine consults. Compared to other, in-person MFM consults across the UPMC system during the same period, these individuals were predominantly Caucasian, younger, and more likely to have public insurance coverage. The most prevalent conditions for which consultations were conducted included diabetes, prior history of preterm labor, hypertension, and preeclampsia.

Caesarean-section rates were comparably high for both groups; fetal mortality was rare for both cohorts as well. Patients who had telemedicine consults showed lower rates of both premature delivery and NICU stays.

Across all telemedicine patients and facilities, 84.4 percent of patients were able to deliver their babies at their local hospital.

In addition to these and other metrics analyzed and reported in the paper[1], the study also examined the cost-savings to patients associated with telemedicine visits in avoidance of lost time at work and travel expenses. In total, the analysis estimates total savings across all patients of $90,103.90, approximately $90.28 per telemedicine consult.

Patient satisfaction surveys were captured from 465 individuals (86.27 percent response rate based on 539 consultations) in 2014 and 2015. Eighty percent of respondents reported being very satisfied with their telemedicine experience, and 83 percent expressed strong confidence in the physician's telemedicine care.

Additionally, "Having a telemedicine visit as opposed to an in-person consult saved 56 percent of the patients over two hours in round-trip driving time. Seventy-four percent said that the telemedicine visit allowed a family member to be present who would not have been otherwise able to attend the appointment. The telemedicine consultation center provided access to 11 percent of patients who would have otherwise forgone care. Ninety-five percent of respondents indicated that they would be interested in participating in future telemedicine visits.

"Our findings provide continuing encouragement that our programs are on the right track, providing needed care to some individuals who otherwise would not receive it. This may be our best approach to providing high-quality MFM care to at-risk mothers and babies who would otherwise not have access. There are few to no downsides to this kind of program that we can discern from our historical perspective," says Ms. Kalocay.

New Services and Future Expansion Plans

Since its inception, the MFM telemedicine program has expanded its services for patients in various areas. One such area is genetic testing and counseling. Samples are drawn at the patient's local provider office or hospital and then are sent to UPMC Magee for analysis. First-trimester screening, noninvasive prenatal testing, and multiple marker screening are available, along with requisite telegenetics counseling sessions with the patient to discuss the results of their testing and help them understand what the information means and what things they likely need to consider if there are adverse findings.

Diabetes management is offered for those with gestational diabetes and includes nutritional counseling and glucose meter education in both one-to-one and group sessions. One-to-one consultation for patients with either type 1 or type 2 diabetes also is a part of the program.

Preconception counseling is another service available for patients, linking them directly with specialists in the UPMC Magee Center for Fertility and Reproductive Endocrinology where they can discuss such options as fertility preservation, in vitro fertilization techniques, early embryo viability testing, and preimplantation genetic screening and counseling.

"Our MFM services will continue to grow and expand their reach. We have gone from having to convince our community doctors and hospitals to use the services to a point now where we are at maximum capacity covering the demand. Our approach to co-managing MFM patients with their local doctors has made acceptance and use of the services easy to replicate as we add new sites," says Ms. Kalocay.

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UPMC Magee OB/GYN Department Appoints New Director of Urogynecology Division

Pamela Ann Moalli, MD, PhD, has been appointed as the new director of the Division of Urogynecology and Pelvic Reconstructive Surgery in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh School of Medicine and UPMC Magee-Womens Hospital. Dr. Moalli was promoted to the division director position, and Halina Zyczynski, MD, the former director, has assumed the role of medical director of Magee-Womens Specialty Services at UPMC Hamot in Erie, Pennsylvania.

Dr. Moalli holds the appointments of professor in both the Department of Obstetrics, Gynecology, and Reproductive Sciences and the Department of Bioengineering, along with secondary appointments as an associate professor at the University of Pittsburgh's McGowan Institute for Regenerative Medicine and the Clinical and Translational Science Institute. Additionally, Dr. Moalli serves as fellowship director for the Female Pelvic Medicine and Reconstructive Surgery Program.

Dr. Moalli earned her doctorate in molecular and cellular biology and her medical degree from Northwestern University as part of its NIH-sponsored Medical Scientist Training Program. She then completed both her obstetrics and gynecology residency and fellowship in urogynecology and reconstructive pelvic surgery at the University of Pittsburgh and UPMC Magee, where she joined the faculty as an assistant professor immediately after completing fellowship training in 2000.

In 2004, Dr. Moalli became the director of translational research in the Division of Urogynecology and Reconstructive Pelvic Surgery, followed by appointment as director of the Female Pelvic Medicine and Reconstructive Surgery fellowship in 2006. In 2007, she was promoted to associate professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences, and in 2016 was named a full professor with tenure in the Department.

Research Focus and Contributions to Science

A distinguished basic science researcher, clinician, and educator, Dr. Moalli and her collaborators operate one of only a few research programs and laboratories in the country that use a laboratory-based approach to study the pathogenesis of pelvic floor disorders, particularly in the context of severe maternal birth injury. In addition, Dr. Moalli has established herself as a national and international leader in biomaterials used to repair pelvic organ prolapse, employing state-of-the-art technology that includes computational models developed by her research group that are providing insights into the mechanisms by which commonly performed surgeries fail to improve patient outcomes.

The primary focus of Dr. Moalli's research has been on prolapse meshes, first defining their impact on the vagina and then transitioning to studying mechanisms of complications. Based on this knowledge, her group is currently working to develop novel, elastomeric meshes with biomechanical properties that more closely match those of the native tissue of the vagina. More recently, she has explored regenerative techniques to rebuild compromised vaginal supportive tissues. The strength of her research group is that it is highly interdisciplinary with expertise in biochemistry, biomechanics, computational analyses, and biomaterials.

The Center for Interdisciplinary Research in Female Pelvic Health (CIRPH)

Dr. Moalli co-directs the Center for Interdisciplinary Research in Female Pelvic Health (CIRPH) with Steven Abramowitch, PhD. The CIRPH is engaged in collaborative studies designed to contribute insights into the pathogenesis, diagnosis, and treatment of pelvic organ prolapse and urinary incontinence. The Center's research priorities primarily focus on the use of biomaterials in urogynecologic procedures, defining mechanisms of failure after reconstructive pelvic surgeries and elucidating the mechanisms of maternal birth injury. Dr. Moalli and her research collaborators have collective expertise in cellular and molecular biology, including both traditional and high throughput platforms, soft tissue mechanics, mechanobiology, tissue regeneration, and immunomodulation.

New NIH R01 to Develop Novel Prolapse Device

Dr. Moalli's latest NIH-funded R01 grant, obtained in April 2019, is a five-year, $2.5 million award that will fund research designed to overcome complications of polypropylene prolapse meshes through the development of novel elastomeric auxetic devices. Dr. Moalli's group seeks to develop a new device designed specifically for the vagina that has high potential to markedly improve the outcomes of prolapse surgeries while minimizing complications.

Leading Research Into Synthetic Materials for Urogynecologic Applications

Dr. Moalli and her research team are international leaders in studies defining the impact of commonly used urogynecologic meshes on the vagina (histomorphologic, biochemical, and mechanical endpoints) in animal models (primate) and women, modifying the host response to improve long-term outcomes and developing meshes that are designed specifically for the material properties of the vagina (current materials are simply hernia meshes remarketed for prolapse surgery as 510K devices). In ex vivo mechanical tests in conjunction with computational analyses, Dr. Moalli's group has clearly demonstrated that prolapse meshes often have markedly unstable geometries with a dramatic loss of porosity with small applications of tension, and that the stresses imposed on the vagina by the mesh have significant regional variability. These effects are driven mainly by modifiable factors, including the pore geometry of the mesh, the degree of tension, and how the mesh is anchored. Indeed, the group's experimental and computational model predictions of the impact of these mechanical effects are confirmed in mesh explants removed from women with mesh complications that demonstrate buckles, folds, and pore collapse. Using ex vivo mechanical tests in conjunction with animal models and computational analyses, the group previously demonstrated that most mesh used for incontinence and prolapse surgery has unstable geometries with a loss of porosity under modest tension. They hypothesize that this is a mechanism for complications (exposures and visceral erosions). The group is currently developing a new generation of meshes based on elastomeric polymers and stable geometries as an alternative to current polypropylene meshes, which plastically deform when loaded. In addition, they are working towards personalized meshes based on 3D modeling of an individual patient's vagina and specific support defects with the idea that it is unlikely that a single mesh type and geometry is an appropriate match for all women with prolapse.

Educational Priorities

In addition to her research and clinical efforts, Dr. Moalli is extensively involved in teaching college and medical students, graduate students, residents, and clinical fellows. Her greatest teaching commitment is to the fellows in the Female Pelvic Medicine and Reconstructive Surgery Program at the University of Pittsburgh. As director of the program, she is responsible for ensuring that the fellows have the appropriate training as clinicians, surgeons, and researchers to rise to the top of their field.

After assuming the role of director of the fellowship program in 2006, Dr. Moalli reorganized the program to provide comprehensive, integrated training in urogynecology, urology, gastroenterology, and colorectal surgery, ultimately achieving full ACGME certification of the program in 2014.

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Recurrent Ovarian Cancer: Combination Therapies and New Clinical Trials

Combination therapies for the treatment of primary and recurrent ovarian cancer along with intraperitoneal administration have garnered some successes in recent years. Basic and translational investigations continue to materialize in the ovarian cancer program at UPMC Hillman Cancer Center. Some of the newest studies have begun to look at various combinations including the use of the toll-like receptor 3 (TLR3) agonist rintatolimod (Ampligen®). Rintatolimod's initial development and use were designed for treating chronic fatigue syndrome and rheumatologic conditions. Since that time, rintatolimod has been taken up by researchers and deployed in clinical trials investigating its immunomodulatory effects for treating a number of diseases, such as HIV/AIDS, colorectal cancer, breast cancer, melanoma, and, more recently, recurrent ovarian cancer.

"Rintatolimod stimulates pathways of the innate immune system that may allow for an increased tumor response when used in combination with other chemotherapy agents such as cisplatin and immunotherapy agents like the checkpoint blockade inhibitors nivolumab or pembrolizumab," says **Brian Orr, MD**, assistant professor of medicine in the Division of Gynecologic Oncology at UPMC Magee-Womens Hospital.

In recent years, ovarian cancer researchers Dr. Orr, along with principal investigator **Robert P. Edwards, MD**, chair of Department Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh School of Medicine and UPMC Magee, and **Anda M. Vlad, MD, PhD**, associate professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, Department of Immunology, University of Pittsburgh, School of Medicine Director, MWRI Flow Cytometry Core Director, have been conducting preclinical studies and early phase clinical trials to test the safety and efficacy of rintatolimod in several combinations with intraperitoneal administration of cisplatin, interferon alpha-2b (IFN), and pembrolizumab to treat cases of recurrent ovarian cancer.

Dr. Vlad's laboratory conducted numerous preclinical studies of the drug combinations in animal models to derive the necessary toxicity, safety, and efficacy data required for advancement to phase 1 studies.

"Combining immunotherapy agents with chemotherapeutic agents and administering them at the same time requires us to determine what effects the chemotherapy agents have on the immune system and how they interact with the immune system modulators we are administering. We want the relationship to be supportive rather than deterimental. Uncovering these drug interactions and the effects of the host immune system was the responsibility of my laboratory," says Dr. Vlad.

"As a field, we have had remarkable success in recent years treating some forms of cancer with the new immunotherapy agents that have been developed, such as the checkpoint blockade inhibitors. However, the unfortunate fact is that only a small subset of cancers and patients will see complete and durable responses. Less immunogenic tumors — cold tumors, if you will — like those seen in ovarian cancer, breast cancer, or colorectal cancer, are still troubling. Finding ways to help improve the immune response with such agents as rintatolimod is one approach we are investigating," says Dr. Orr.

The First Phase 1 Study of Rintatolimod for Recurrent Ovarian Cancer Shows Promise

In what is likely the first clinical trial[1] ever to investigate the use of rintatolimod for recurrent ovarian cancer in combination with several other agents administered intraperitoneally, Drs. Edwards, Orr, and Vlad, in conjunction with collaborators at Hemispherx Biopharma (the manufacturer of Ampligen) and Roswell Park Comprehensive Cancer Center, began the first combination therapy trial including rintatolimod in 2015. The trial was designed primarily to assess safety and efficacy, with patients receiving various combinations of treatment agents in the various arms of the study.

"The first cohort of patients received only intraperitoneal (IP) cisplatin. The second cohort received IP cisplatin and rintatolimod. The third group received IP cisplatin, rintatolimod, and also interferon alpha. Each group was assessed for signs of toxicity and potential responses in order to develop a reasonable likelihood of safety and efficacy prior to pursuing a phase 2 study," says Dr. Orr.

Patients in the various cohorts also received the COX-2 inhibitor celecoxib as part of the immunotherapy cocktail. This was done because, in preclinical studies in the laboratories of Drs. Edwards and Vlad, and a colleague at Roswell Park, Dr. Pawel Kalinski, the use of celecoxib showed an increase or enhancement in tumor response.

Early in 2019, the study researchers announced that the trial had met its primary endpoints and that a new phase 2 investigation would be launched in 2019.

"Building upon the preclinical data that Dr. Vlad's laboratory was able to uncover, we were able to determine that rintatolimod is safe and was well-tolerated by the study participants, so we immediately began plans for our next trial," says Dr. Orr.

Drs. Orr, Vlad, Edwards, and colleagues are currently finalizing their manuscript of findings for the first trial, with publication likely to occur in the near future.

New Phase 2 Study Seeks to Expand Rintatolimod Findings in Recurrent Ovarian Cancer

In early 2019, the phase 2 study[2] of rintatolimod began recruiting patients at UPMC Magee and UPMC Hillman Cancer Center. As of September, 2019, six patients have been enrolled in the trial, with the ultimate goal of obtaining 45 participants in the study.

For the new study, participants with recurrent ovarian cancer that is platinum-sensitive will receive a combination therapy consisting of intensive locoregional intraperitoneal cisplatin with IP rintatolimod and an IV infusion of pembrolizumab. Six treatment cycles will be given at three-week intervals. After treatments, patients will have cytoreduction surgery approximately four weeks after the fourth treatment interval.

"From an outcomes standpoint, we will be looking at the objective response rate at 13 weeks posttreatment. Additionally, we will monitor progression-free survival, and any changes in the patient's number of CD8+ and CD3+ cells in tumor samples and peritoneal fluid," says Dr. Orr.

Beyond these study endpoints, Dr. Vlad's translational laboratory will obtain and analzye, throughout the treatment process, intraperitoneal tissue, blood, and fluid samples to evaluate the impact of the combination regimens have on the tumor immunologic micro-environment and to search for biomarkers that may help predict or differentiate likely responders from nonresponders.

"By obtaining samples from the vicinity of the tumor in the intraperitoneal cavity at various points in time, we should be able to assemble a dynamic view of the local tumor microenvironment in the context of responses to treatment or regression over time. This kind of data will add a new dimension of power to our analysis by giving a dynamic picture of what is happening over time in our participants," says Dr. Vlad.

"Pittsburgh has been an immunotherapy hub for a long time. The breakthroughs we have made over the years, coupled with the resources available at our institutions, will continue to allow us to answer some of these very difficult questions in cancer treatment and research, such as how to make nonresponders responders, and how to turn cold tumors into hot ones. This is our devotion, and with the generous help and perseverance of our patients, I think we will ultimately be successful," says Dr. Orr.

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More About Dr. Orr

Dr. Orr is an assistant professor at UPMC Magee in the Division of Gynecologic Oncology. In addition to clinical activities of surgery and chemotherapy for gynecologic cancer patients, Dr. Orr is active in clinical and translational research. He is active as principal investigator or co-PI on several investigator-initiated clinical trials. Dr. Orr also is the site principal investigator for the UPMC Hillman Cancer Center on several multi-institutional clinical phase 1, 2, and 3 trials with the collaborative NRG/Gynecologic Oncology Group. Dr. Orr additionally is involved in resident and fellow education with mentorship in clinical, research, and career development. Dr. Orr's research interests are in clinical and translational clinical trial development for ovarian, endometrial, cervical, and vulvar cancers. His specific chemotherapy research interests are in the immunotherapy and targeted therapies.

More About Dr. Edwards

Dr. Edwards is a professor of medicine and chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh School of Medicine. Dr. Edwards also is the executive vice chair of gynecologic services at UPMC Magee and the principal investigator of the ovarian cancer SPORE grant at UPMC Magee and UPMC Hillman. Dr. Edward's research interests include cervical and ovarian malignancies, with a special emphasis on the use of intraperitoneal chemotherapy and novel immunotherapies to treat various gynecologic cancers.

More About Dr. Vlad

Dr. Vlad is an associate professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences and the Department of Immunology at the University of Pittsburgh School of Medicine. She also is the Magee-Womens Research Institute Flow Cytometry Core Director. Dr. Vlad's research laboratory explores mechanisms of disease pathogenesis and immune surveillance in ovarian cancer and precursor lesions, and tests novel preventive and therapeutic approaches using a combination of highly versatile preclinical models and clinical specimens. Through collaborations with clinicians at UPMC Magee, the lab is working on identifying mechanisms of early ovarian carcinogenesis from cancer precursor lesions. Ongoing projects focus on the development of new combination therapies for metastatic ovarian cancer.

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