

UPDATES IN GYNECOLOGY

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Message from the Chairman

Dear Colleagues,

In this new edition of *Updates in Gynecology*, I am pleased to share with you recent highlights from our research and clinical programs. In the pages that follow, you will learn more about the efforts of our Pregnancy Recovery Center to help women and newborns who are struggling with opioid use disorders, and new research tackling aspects of Hepatitis C virus treatment and prevention. Our Maternal Fetal Medicine division continues to break new ground in treatment and research, while the Center for Medical Genetics and Genomics has recently developed a new hereditary cancer screening panel and a targeted exome sequencing test that holds particular value for the pediatric population. In this issue we also feature the Magee-Womens Research Institute, a driving force in women's health research with a mission and reach that spans the globe.

Beyond the efforts highlighted in this issue, our department is involved in two new immunotherapy trials. The first is a cervical cancer trial sponsored by Iovance Biotherapeutics that will test the efficacy and safety of a cell transfer therapy using an autologous tumor infiltrating lymphocyte (TIL) protocol for recurrent or metastatic cervical carcinoma. A second trial in recruitment is investigating pre-invasive HPV-related vulvar intraepithelial neoplasia, a difficult-to-treat cancer affecting approximately 10,000 women a year. The trial will use a gene therapy protocol previously tested in a trial for cervical dysplasia, and Magee is the lead site for this new investigation.

At Magee, our department has finished building and recruiting staff for a full-service obstetrics and gynecology program based at UPMC Hamot in Erie, Pennsylvania. The program has become a second hub for the comprehensive primary and specialty obstetric and gynecologic care that Magee is known for in the greater Pittsburgh region. The program extends our reach to patients in northwestern Pennsylvania, southwestern New York, and northeastern Ohio, and provides women and newborns with convenient access to a full spectrum of care.

Finally, I would like to welcome to the department our two newest faculty members. **Ronald Buckanovich, MD, PhD**, and **Lan Coffman, MD, PhD**. Doctors Buckanovich and Coffman are both fellowship-trained hematologist-oncologists pursuing some of the latest novel research into aspects of ovarian cancer biology and therapeutic treatments. You can read more about their backgrounds and work further on in this newsletter.

It is a great privilege to lead such a varied department and dedicated staff, and to share with you our work on some of the biggest challenges facing gynecologic medicine today.

Respectfully,

Robert P. Edwards, MD

Chairman, Department of Obstetrics, Gynecology, and Reproductive Sciences
Co-Director, Gynecologic Oncology Research, Magee-Womens Hospital of UPMC

The Pregnancy Recovery Center

Addressing Opioid Addiction

The opioid epidemic has had a profound impact on pregnant women and their children. To address the increasing prevalence of opioid abuse during pregnancy, the Pregnancy Recovery Center (PRC) at Magee-Womens Hospital of UPMC was launched in 2014 to provide a patient-centered medical home for the treatment of pregnant and postpartum women with opioid use disorder (OUD). **Elizabeth E. Krans, MD, MSc**, is an obstetrician/gynecologist and one of six buprenorphine treatment providers at the PRC. In addition to providing OUD treatment services for pregnant and postpartum women, Dr. Krans also is pursuing several NIH- and industry-funded research studies designed to improve the health care delivery process for pregnant women with OUD and decrease high-risk health behaviors associated with substance use.

Pregnancy Recovery Center at Magee-Womens Hospital of UPMC

Medical Director, Michael England, MD

Research Director, Elizabeth Krans, MD, MSc

Clinical Director, Stephanie Bobby, BSN, RN

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“Pregnancy is a unique time for all women. We are interested in how we can utilize pregnancy as a window of opportunity to impact behavior change, as well as understand how to optimize OUD treatment services to positively impact the recovery process well beyond delivery. Women are both physiologically different and behave differently during pregnancy, and it is incumbent upon providers to recognize these differences and treat them accordingly. This is why we have a robust research program at Magee — to unlock what these optimal treatment pathways ought to be for addiction itself, but also to more effectively address comorbidities and high-risk health behaviors associated with substance use,” says Dr. Krans.

Clinical Components of the Center

Since opening in 2014, the Pregnancy Recovery Center has treated a growing population of women (more than 300 to date) with OUD during and after pregnancy with comprehensive, women-centered services, including buprenorphine inductions and maintenance therapy, behavioral therapy, prenatal and postpartum care, and social services support. A buprenorphine-only program, the center has six physicians, including Dr. Krans, who are all practicing OB/GYN specialists, as well as a full-time social worker and two full-time RNs who provide additional case management and counseling support for patients. Additionally, the program boasts two peer navigators — women with a past-lived addiction experience who provide another layer of support and compassion to individuals during their recovery process. “Our success at the PRC is entirely due to our team of clinical care providers who are truly devoted to helping this population achieve success in their recovery and as moms,” says Dr. Krans.



Elizabeth E. Krans, MD, MSc

In the spring of 2017, the PRC expanded its services with the addition of the Womens Recovery Center to meet the growing demand for services. This program provides ongoing treatment for women after delivery to minimize disruptions in treatment and maximize the potential for recovery, as continuity of care and strong patient-provider relationships are such an important part of the overall process. The center also accepts nonpregnant women into the treatment program at any stage of life. “We provide women-centered care for our patients, and include services such as contraceptive counseling, intimate partner violence or abuse screening, and child care, on top of all of the other comprehensive substance abuse treatment services provided by the PRC,” says Dr. Krans.

Expanding Services and Options System-Wide

OUD treatment services for pregnant and nonpregnant women are also expanding across the UPMC system in a hub-and-spoke model to better address the growing opioid-dependent population in outlying rural areas across the UPMC system. “There’s a higher prevalence of opioid abuse in rural areas, and these areas typically have fewer resources,” says Dr. Krans. To address this disparity, the PRC is opening a satellite program at UPMC Hamot in Erie, Pennsylvania. Telemedicine services have also been established at additional rural sites within the UPMC system to connect providers and patients to Dr. Krans and her colleagues at the PRC at Magee. “Our goal is to disseminate what we’ve been able to accomplish at Magee to benefit as many women as possible, by either replicating our programs elsewhere or, when that is not feasible, providing the remote support needed for an exponentially rising population of women with opioid use disorders,” says Dr. Krans.

Hepatitis C Transmission and Treatment During and After Pregnancy — New and Novel Research

Hepatitis C Virus (HCV) is a highly prevalent comorbidity in the population of opioid-dependent pregnant women at approximately 60 percent, with a perinatal transmission rate of approximately five to eight percent. More than 28 percent of newly diagnosed cases of HCV occur during pregnancy. Unfortunately, fewer than two percent of pregnant patients start treatment for HCV within one year after delivery. Clinicians and researchers from the PRC and other areas at Magee are currently investigating several lines of research into HCV transmission and treatment during and after pregnancy, with implications for both mother and baby.

One study,¹ a phase 1 clinical trial led by primary investigator **Catherine Chappell, MD, MSc**, is investigating the possibility of preventing perinatal transmission of the virus by treating the mother for HCV during her pregnancy. This pharmacokinetic trial is the first of its kind to begin to understand the safety of HCV treatment during pregnancy. The trial has been ongoing for the past year and is supported by Gilead Sciences, Inc., who is supplying Harvoni®, their direct-acting antiretroviral medication. Dr. Chappell also has received additional NIH funding to support the ongoing trial. The trial is evaluating the safety of a 12-week treatment regimen during the second and third trimester.



Robert H. Gedekoh, MD, and Michael V. England, MD

A second study,² with Dr. Krans serving as primary investigator, is set to begin in the near future. This investigation will begin in the immediate postpartum period and combine an HCV medication regimen with buprenorphine or another opioid pharmacotherapy treatment the patient is receiving in the PRC. “We know that these patients with HCV should also be receiving treatment for their substance abuse disorder, so our study will combine both therapies at the same time immediately after the patient gives birth,” says Dr. Krans. Dr. Krans’ study is also supported by Gilead Sciences but will use a different direct-acting antiretroviral — Eplusera® — which is a pan-genotypic HCV drug capable of treating all the genotypes of HCV. Patients enrolled in the study will receive comprehensive care at the PRC from obstetricians, substance abuse professionals, hepatologists, and pediatricians.

Another related study, led by **Hyagriv Simhan, MD, MS**, who is the director of the Division of Maternal Fetal Medicine at Magee, is examining in an observational study the risk factors for perinatal transmission of the HCV. This prospective study, part of a national multicenter research project coordinated by the Maternal Fetal Medicine Units (MFMU) Network, seeks to evaluate and stratify the risk factors of HCV transmission from mother to baby. The implications of the study may help to determine in the future which women are most at risk for transmission, what the risk factors are, and who may benefit the most from therapy during pregnancy to prevent transmission if and when medication therapy for HCV during pregnancy becomes a common modality.

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Maternal Fetal Medicine at Magee: Managing and Mitigating Risk

The Division of Maternal Fetal Medicine (MFM) at Magee, under the direction of **Hyagriv Simhan, MD**, encompasses a comprehensive maternal fetal medicine clinical program along with specialty services that include the Fetal Diagnosis and Treatment Center led by **Stephen Emery, MD**, who also heads the Center for Innovative Fetal Intervention, and the Center for Advanced Fetal Diagnostics. Research and training are also integral to the division, which sports a robust, multidisciplinary research program attracting substantial grant support, and a three-year fellowship program currently supporting the training of new MFM fellows each year.

“In a given year, we typically handle 1,000 deliveries and offer consultations on nearly three times that many cases from all across UPMC’s operating geography. We are responsible for the Perinatal Referral Service — staffed 24/7 by one of our maternal fetal medicine specialists who can answer questions and accept transfers. At any given time, we have approximately 200 patients in our prenatal practice,” says Dr. Simhan.

Making Pregnancy Safer for All Mothers

There is an unfortunate trend in the United States over the last 20 years pointing to an increasing level of danger during pregnancy for both mothers and babies. Maternal mortality rates show an upward trajectory, despite advances in health care as a whole. Some of this is directly attributable to better data capture and measurements related to maternal mortality rates. “Some of these deaths were already occurring; now we are better able to attribute them,” says Dr. Simhan. But there certainly are other factors at play that are driving an uptick in maternal mortality rates. The mother’s age at pregnancy has steadily increased over the last several decades. The prevalence of rates of obesity across the population have increased, along with other comorbidities such as type 2 diabetes, cardiovascular disease, and illicit drug use. And then there are factors attributable to socioeconomic status, race, and geography that are proving to be significant factors in who receives care, when, and to what degree.

For Dr. Simhan and his colleagues in the division, the emphasis was and will always be on the health of the mother, not just her baby. Maintaining and improving the health of the mother who is experiencing a high-risk or complicated pregnancy is

the best way to preserve, protect, and ensure the health of the fetus — during and after pregnancy. The expertise of care at Magee affords the highest level of care for medical complications and critical illness during pregnancy, with a dedicated obstetrical ICU on call for patients in need.

“Our prenatal program is the center of our world, but we render care and consultations over a large geographic area, co-managing patient care with doctors and midwives in the community. Ensuring safe pregnancies is our mission. We want patients to deliver in their own communities, but when warranted, we can facilitate transfer to Magee and then return the mother and baby back to their community for their routine postpartum care and follow-up,” says Dr. Simhan.

Much, if not all, of the research and clinical care initiatives by the physicians and scientists of the division lead back to the goal of making pregnancy safer for women, and improving outcomes for those at a high risk for complication. Several new clinical programs and recently funded research projects are helping to drive forward improvements in patient care.

Extending the Reach of MFM Through Telemedicine

Telemedicine has been a potent force of change in the world of health care. Its ability to extend the reach of high-quality care programs to outlying areas, or those areas lacking the robust infrastructure and specialized capabilities of large academic medical centers and the like, has proven beneficial for numerous specialties and subspecialties. And it’s true for the world of maternal fetal medicine as well. As logistical, payor, and legislative developments move toward allowing greater flexibility for the use of telemedicine, its acceptance will surely grow.



Hyagriv Simhan, MD



Members of the Maternal Fetal Medicine Division: Front Row (L to R): Hyagriv Simhan, Arun Jeyabalan, Maisa Feghali, Katherine Himes, Jillian Grove, Steve Caritis; Back Row (L to R): Jacob Larkin, Francesca Facco, Sara Sakamoto, Carrie Weaver. (Not pictured: Sami Makaroun, Kristiina Parvianen-Yang, Devon Ramaeker, Janet Catov, Robin Grandley, Carl Hubel.)

UPMC has been an early adopter and pioneer in the use and development of telemedicine technologies. The MFM telemedicine program at Magee began in 2011, supporting patients and clinicians at UPMC Northwest. “We quickly expanded our program to our community hospitals in Bedford, Hermitage, Altoona, and Uniontown, all of which are significant distances from Magee-Womens Hospital in Pittsburgh,” says Wendy Kalocay, director of MFM telemedicine services. General obstetricians on site at community hospitals provide their patients with primary obstetrical care but can rapidly consult with MFM specialists at Magee when needed. Both inpatient and outpatient telemedicine consults are part of the MFM telemedicine program, and transfers for emergency care to Magee can be expedited through the telemedicine platform when required.

Obstetrical ultrasound is critical to the maternal fetal medicine specialty and is a core component of the MFM telemedicine platform. An OB ultrasound physician at 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 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 trained at Magee. They spend several weeks in OB ultrasound training.

This ensures everyone has the same qualifications and standards as the diagnosticians at Magee,” says Ms. Kalocay.

Novel Research, New NIH-Funded Studies, and Part of the MFMU Network

Collaborative, multidisciplinary research is a trademark of the Division of Maternal Fetal Medicine at Magee. The division has been part of the Maternal Fetal Medicine Units (MFMU) Network for more than 25 years of its existence and is a part of the network in its current five-year grant cycle. Dr. Simhan is the principal investigator of the current MFMU project, and he is leading Magee in several new studies within the network and planning for several new investigations in the future focused on the prevention of preeclampsia and maternal postpartum hemorrhage prevention.

Hepatitis C Transmission During Pregnancy

With the expanding opioid epidemic in the United States comes increasing rates of the hepatitis C virus (HCV) among opioid users and, consequently, the risk of transmission of the virus from mother

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The Center for Innovative Fetal Intervention

The Center for Innovative Fetal Intervention (CIFI) at Magee-Womens Hospital of UPMC treats some of the rarest, most complex prenatal conditions amenable to in utero surgical intervention. For the past 11 years, the center has been under the direction of **Stephen Emery, MD**. At its core, the center is a multidisciplinary, highly collaborative program that treats fetuses with structural or functional anomalies of multiple organ systems.

One of the defining characteristics of Dr. Emery's program is that it resides within a women's hospital and is directed by a maternal fetal medicine specialist. This puts a focus squarely on the safety of the mother as well as the health of the fetus.

Part of the NAFTNet Collaborative

The CIFI at Magee is a member of the North American Fetal Therapy Network (NAFTNet), an association of 33 medical centers in the United States and Canada that collaborate on clinical research for these rare conditions. Dr. Emery is currently the chair of the steering committee, which puts him at the center of managing its research agenda. Because of the rarity of most conditions that Dr. Emery and his colleagues within NAFTNet see, no one center alone has the volumes to drive forward the understanding of the natural history of these conditions and improve upon their outcomes.

What helps NAFTNet excel as an organization, explains Dr. Emery, is its multicenter, multidisciplinary collaborations. A diverse collection of specialties and subspecialties is represented and brings collective expertise and wisdom to bear upon the research and practice of fetal interventional medicine. There also is a tremendous degree of transparency among the members that allows its collaborative nature to prosper. "NAFTNet, through the work of the collaborative centers, is changing the way we practice by generating evidence-based recommendations. It is helping to improve outcomes on a national level, perhaps even a global level. This impact can be seen

in recent recommendations regarding the management of early stage twin-twin transfusion syndrome generated from a multicenter NAFTNet research study."

Twin-Twin Transfusion Syndrome

A rare but devastating condition that affects approximately 10 percent of twins who share a single placenta (monochorionic twins), twin-twin transfusion syndrome (TTTS) occurs when one fetus donates its blood volume ("donor") to the other ("recipient") through shared blood vessels. Left untreated, morbidity and mortality rates are very high. "We've known for a number of years that intervention for high-stage TTTS improves outcomes, leading to higher survival rates. But there was always a question about what to do with early stage disease, stage I: observe or intervene? Some felt that most cases regressed on their own with good outcomes. But we all know of cases where they progressed rapidly with terrible outcomes. So the question was: How to manage stage I disease?" says Dr. Emery.

To answer this question, Dr. Emery at Magee, along with the other NAFTNet partners, undertook a study of stage I TTTS. The study included 124 cases. Forty percent were managed expectantly. Twenty-four percent underwent amnioreduction, and 36 percent received laser therapy. The results of the study were unequivocal: 70 percent of cases under observation worsened, and with these cases was an accompanied worse prognosis. Those cases where



intervention occurred were associated with a decreased risk of fetal loss. “Our findings suggest that intervention is superior to observation. To be sure, further research is warranted, but our findings should, in the short-term, lead to a shift toward discussing early intervention for stage I disease with our patients,” says Dr. Emery. “The combination of early diagnosis and early intervention will likely lead to the best possible outcomes for TTTS, more than advances in equipment or surgical technique: catch it early, and treat it early.”

Reevaluating the Efficacy of an Old Approach to Fetal Hydrocephalus

Fetal hydrocephalus carries a terrible neurologic prognosis with approximately 50 percent mortality, while those who survive are devastated neurologically. In the 1980s, alongside the growth of ultrasound, ventriculoamniotic shunting was attempted as an intervention for cases of fetal hydrocephalus. However, it was quickly abandoned because of terrible outcomes. The International Fetal Medicine and Surgery Society (IFMSS), of which Magee is currently a member, was the original body that put a moratorium on the use of the procedure. “Ultrasound technology at the time did not allow for the resolution needed for accurate diagnosis of which fetus could benefit and which could not. We simply did not have the technology in place to make it work, so the field abandoned the practice,” says Dr. Emery.

Today, the ability to diagnose with precision is vastly superior. Because of this, Dr. Emery, through NAFTNet and the University of Pittsburgh, is reevaluating the use of in-utero shunting for fetal hydrocephalus — specifically aqueductal stenosis (AS), or obstruction of the aqueduct of Sylvius connecting the third and fourth ventricles in the fetal brain. Cerebral spinal fluid (CSF) continues to be produced but cannot circulate due to the stenosis, allowing pressure to continually build until brain injury occurs. Dr. Emery and NAFTNet colleagues will first determine their ability to make an accurate diagnosis of AS in real time. If possible, the next step is to determine whether shunting will bypass the area of stenosis and drain the CSF from the ventricle into the amniotic cavity, thereby decreasing pressure and preventing brain injury. “We’re approaching these studies in a multidisciplinary, multicenter manner that leverages all of the various specialties’ expertise in order to, we hope, revive an older procedure with vastly better outcomes in a scientifically rigorous fashion.”

These studies build off of previous work by Dr. Emery and colleagues at Magee that examined the ability to accurately diagnose isolated aqueductal stenosis prenatally, as well as analysis of the original shunting procedures performed several decades prior.^{2,3} The new NAFTNet study is a much larger trial aimed at prospectively demonstrating the ability to accurately diagnose AS. Beyond these investigations, Dr. Emery also has been involved in the design and development of a new shunt device for use in the treatment of AS.

Engineering a Novel Shunt Device for AS

Collaborating with bioengineers at the University of Pittsburgh Swanson School of Engineering, Dr. Emery and a group of colleagues have designed a new shunt⁴ for use in AS that is designed to meet



very specific performance characteristics and uses materials that have already been approved for other purposes by the U.S. Food and Drug Administration (FDA).

“Because my goal is to do these procedures with a minimally invasive, ultrasound-guided technique, the device had to be designed in such a way as to facilitate this kind of procedure. We have a prototype and are currently working with the McGowan Institute for Regenerative Medicine on an animal model of hydrocephalus.” Dr. Emery’s shunt research seeks to understand the efficacy of the device while at the same time testing dose-response by varying the time interval of intervention and placement of the shunt in the subject. “Ultimately, we are after FDA approval, manufacture, and open label trials. All of this is coming out of Magee and is the product of many collaborations between individuals and entities within UPMC and the University of Pittsburgh. These resources make this kind of work possible,” says Dr. Emery.

Fetal Myelomeningocele — C-section vs. Vaginal Birth

For years it was thought that babies with spina bifida had to be delivered by Cesarean section. However, there was little to no good evidence to support this hypothesis. Studies conducted in the 1980s to support the use of C-section for myelomeningocele babies were not designed well, comparing babies who were prenatally diagnosed and born at a tertiary medical center via C-section with babies who were born at home.

In 2016, Dr. Emery and colleagues from the Department of Pediatric Neurosurgery at Children’s Hospital of Pittsburgh of UPMC undertook a retrospective study⁵ of all myelomeningocele births within UPMC from 1995 to 2015, looking at the difference between functional

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A Global Mission to Improve Health Care: The Magee-Womens Research Institute



As the largest research institute in the country dedicated to women's health, Magee-Womens Research Institute (MWRI) has a broad but focused platform for impacting the lives, health, and wellness of women and children. This is not a local or regional goal. It is one of global proportions that extends from the individual to the community at large, indeed affecting entire populations. "We look at population health through the lens of women's health because so much of what happens to individuals in early human development and pregnancy, and consequently society at large, is affected by the health of the mother," says **Michael Annichine**, chief executive officer of the Magee-Womens Research Institute.

Transdisciplinary research is the norm. The breadth and depth of research at the institute covers everything from reproductive development to fertility, infectious diseases, oncology, gynecology, pregnancy and neonatology, women's cancers, and women's wellness. "It should be noted, however, that research is not our goal. Research is our tool to advance knowledge in the fields of reproductive science and women's health," says **Yoel Sadovsky, MD**, executive director of the institute.

The problems that the researchers at MWRI are working to solve are often an intertwined knot of complexity, where individual health drives the health of the community and populations, and forces such as socioeconomic status, race, geopolitical currents, cultural significances, and environmental factors all combine to influence the health and wellness of every woman, man, and child no matter where they live. "What happens to women during pregnancy, and happens to the fetus during pregnancy, has lifelong implications for the health and wellness of the individual, female or male. Women carry the pregnancy of males and females, and thus 100 percent of humankind. We feel very strongly that through women's health we can really change wellness worldwide," says Dr. Sadovsky. This idea that the future health of individuals and communities is directly related to a women's health before and during pregnancy is encapsulated in the institute's 9-90™ vision.

9-90 — A New Paradigm

The idea is a simple one, yet the consequences are potentially vast. What occurs to the mother and fetus during the first 9 months of pregnancy has massive implications for the health and development

of both during their next 90+ years of life. 9-90 research seeks to better understand fetal development, how the health of the mother during pregnancy affects the baby in utero, and how those in utero conditions impress upon the long-term health outcomes of individuals. "We believe that the key to optimal long-term health and wellness for individuals and populations begins in utero. Intra-uterine nutrition, the health status and comorbidities of the mother, environmental stressors, fetal anomalies, and the like all conspire in yet unknown ways to set the trajectory of an individual's health for a lifetime," says Dr. Sadovsky.

To that end, this idea of 9-90 research cuts across numerous areas of investigation, from reproductive development to pregnancy and fetal development, reproductive physiology, nutrition, and fertility and genetics. "We are beginning to grasp a better understanding of how and what happens during those crucial first 9 months of life affects the next number of decades, and much of our research plays into this central tenet of the institute," says Mr. Annichine.

The Impact of Research — Recent Highlights, New Studies, and Complex Challenges

The impacts of research being conducted at the Magee-Womens Research Institute are being felt now, locally, nationally, and around the world. One such endeavor, spearheaded out of the Magee-led international Microbicide Trials Network (MTN), are studies and interventions to reduce the transmission of the HIV virus. Clinical trials of the antiretroviral dapivirine vaginal ring have not only been shown to be safe, they have also been shown to cut the transmission rate of HIV by almost 30 percent. Additional studies are ongoing and planned by the MTN that will explore the usage of the dapivirine ring in women under the age of 18. "If the ring is approved for women older than age 18, it's imperative that we have the data in hand to show that the ring is safe to use in younger women as well," says **Sharon Hillier, PhD**, principal investigator of the MTN, and professor and vice chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Pittsburgh. "HIV doesn't distinguish between a 16-year-old and an 18-year-old. Access to safe and effective HIV prevention shouldn't either. Young women of all ages deserve to be protected."

There are many new research endeavors continually springing to life at the institute, chasing answers and solutions to complex challenges in the world of breast and ovarian cancer. Ovarian cancer continues to be a high-priority target to better understand ovarian biology,



Michael Annichine

tumor developmental pathways, and metastatic disease, and how to prevent it in the first place. Also on the ovarian cancer front is new research by **Anda M. Vlad, MD, PhD**, who is investigating novel preventive and therapeutic approaches to ovarian cancer using vaccines, biologics, and anti-PD-L1 therapies. Dr. Vlad, along with **Xin Huang, PhD**, and other colleagues also are exploring a blood-based biomarker test that can analyze the presence of microRNA genetic material present in cases of endometriosis-associated ovarian cancer. Earlier diagnosis of ovarian cancer will be crucial to improving outcomes and saving lives, and Dr. Huang's current animal models are a promising step in that direction.

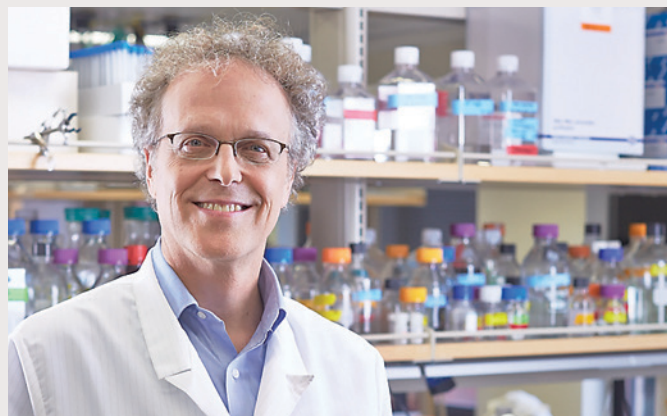
In the realm of premature ovarian insufficiency, institute researcher and genetics expert **Aleksandar Rajkovic, MD, PhD**, is currently studying the underlying genetic factors central to premature aging of the ovary and any implications toward fertility and ovarian function, and consequently, hormone production and early menopause.

A recent \$5 million grant from the Richard King Mellon Foundation is allowing researchers at the institute to grapple with the continual problem of rising infant mortality rates and associated racial disparities in the Allegheny County and Pittsburgh area. Dr. Sadovsky is the principal investigator of this multifaceted study, in collaboration with the University of Pittsburgh and the RAND Corporation. Their work focuses on leveraging and improving the use of the Magee Obstetrical Maternal Infant (MOMI) Database, which is overseen by **Janet M. Catov, PhD, MS**, who also is collaborating with Dr. Sadovsky on the building of a new pregnancy biobank, fostering new basic research into the antecedents and causes of infant mortality, and better prediction of those at higher risk. "In broad terms, approximately 75 percent of the causes of infant mortality have their origin in events before birth — issues such as fetal anomalies, preterm birth, and maternal diseases during pregnancy. Understanding the mechanics and interplay of these and other factors is how we think we can improve upon mortality rates," says Dr. Sadovsky.

Kyle Orwig, PhD, currently is involved in exciting research into fertility preservation for prepubescent children who must undergo chemotherapy or radiation treatments for cancer, potentially preserving their fertility options in the future. Dr. Orwig also was awarded a new five-year, \$1.05 million T32 training grant from the NICHD to provide ongoing graduate and postdoctoral student training in reproductive biology and fertility preservation.

Technological Advancements

A growing focus of the institute is how to leverage its collective capacity to change and improve health outcomes through the development of technologies and pathways to bring new modes of care to the marketplace. In just the last 12 months, researchers at the institute have filed six patents and 13 invention disclosures, with many more ideas and projects in the development pipelines. Several recent examples of technology development include a smart phone app: the My Healthy Pregnancy app was developed and piloted in a lower-income Pittsburgh community that had traditionally not utilized the health care system, and it generated a high level of patient/provider engagement. If successful in broader applications, community engagement could increase, patient quality-of-care may increase, and health systems could very well realize cost-savings by avoiding certain instances of emergency department visits, all through a noninvasive smart phone application designed to



Yoel Sadovsky, MD

allow for better monitoring and communication between the patient and their doctor.

Researchers at the institute have also been working on a noninvasive prenatal testing platform that can allow for fetal testing through the blood of the mother, avoiding the need to do chorionic villus sampling or an amniocentesis in certain circumstances. This type of testing affords many benefits to both mother and baby, reduces false positives, and has increased accuracy. In a similar vein, a pilot study is currently in progress to test the efficacy of a noninvasive test for necrotizing enterocolitis (NEC) in infants, particularly in preterm births where the prevalence and mortality rates can be very high. "If we can find those infants with the condition much earlier in the disease course, we feel that we can significantly improve outcomes," says Mr. Annichine.

Leading the Way to New Discoveries

In October 2018, Magee-Womens Research Institute will convene the inaugural 9-90 Research Summit in Pittsburgh. The two-day, multidisciplinary conference on the new frontiers of women's health will see 500 of the world's leading scientists and science enthusiasts gather and discuss where the research of tomorrow needs to go to shape the future face of health care — to make the shift from developing treatments to developing preventive strategies and cures. "Our goal with the conference is to focus on new visions and collaborations across disciplines. We don't want to talk about the science of yesterday but rather what we collectively need to be doing in the future," says Mr. Annichine.

The inaugural 9-90 conference will also see the presentation of the first Magee Prize, a \$1 million award to the best collaborative research project proposal by any individual or group in the world. "Collaboration accelerates discovery. As national and international leaders in women's health research, we felt an obligation to help spur the next great idea, the next breakthrough discovery that can fundamentally alter the landscape of women's health. That's the objective of the Magee Prize," says Mr. Annichine.

Learn More About the Institute

For more information about the 9-90 Research Summit and the Magee Prize, or general information about the institute and its current research portfolio, and more detailed information about the research studies summarized in this article, please visit MageeWomens.org.

The Center for Medical Genetics and Genomics: New Research and Clinical Advances

Originally founded as the Center for Medical Genetics in the early 2000s by W. Allen Hogge, MD, the renamed Center for Medical Genetics and Genomics has continued to expand its role and mission, providing a range of diagnostic screening and genetic counseling services as well as cutting-edge research for both some of the most common and the rarest of illnesses and conditions.

Aleksandar Rajkovic, MD, PhD, currently serves as medical director, as well as being a driving force in genetics and genomics research within the Department of Obstetrics and Gynecology and the Magee-Womens Research Institute. **Ed Smith, MS, MBA**, is the administrative director of the center, with a background in genetic counseling. Along with Dr. Rajkovic and colleagues, Mr. Smith is responsible for the strategic planning and operations of the center and its day-to-day operations.

Clinical Programs and New Screening Tests

The Center for Medical Genetics and Genomics encompasses a robust collection of services and testing for adults, and collaborates extensively on pediatric testing with labs and clinicians at Children's Hospital of Pittsburgh of UPMC. The center sees and counsels well over 4,000 adult patients each year and collaborates with many specialty areas throughout the UPMC system on patient screening and counseling, such as the Center for Innovative Fetal Intervention and the UPMC CancerCenter. The laboratories of the center perform testing for a full spectrum of conditions, including more than 3,600 molecular testing procedures, more than 7,000 pregnancy screening tests, and more than 17,000 cytogenetic tests each year.

Telemedicine programs are also in place and expanding, allowing the center to triage and reach patients for counseling services in outlying areas that would otherwise be burdensome for patients to travel from to the center's main location at Magee-Womens Hospital of UPMC in Pittsburgh.

New Testing for Hereditary Cancers

Progress is something inherent in the work of the Center for Medical Genetics and Genomics. Research, testing protocols, patient counseling, and outreach all evolve and expand as the knowledge base unfolds over time and patient populations and their needs shift and grow. Adapting to and meeting these needs head-on is a hallmark of the center and its research and clinical staff.

In the next several months, the center will be launching a new hereditary cancer screening panel designed to answer genetic variant questions for patients with personal or familial histories of breast, ovarian, colorectal, and other cancers. Mr. Smith explains that the rationale for this hereditary cancer panel,

which screens and sequences 44 individual genes in one test, is to simplify the testing regimen for the patient and at the same time greatly expand the flexibility clinicians have in analyzing the patient's genetic profile. "With our patient population, we really wanted to develop a test that gives maximum flexibility. While we sequence 44 genes, a clinician may only be interested in 9 or 10, depending on the clinical applicability to the patient. Using software on the back-end, we are able to carve up the panel into a number of specific gene groupings that best address the clinical needs of our referring providers and their patients. We don't have to create a new test for each group, which leads to resource savings in time and cost, flexibility, and a consistent workflow," says Mr. Smith.

Exome Sequencing

In the pipeline for a probable launch in the early part of 2018 is an exome sequencing panel that will concentrate on 5,000 of the approximate 19,000 to 20,000 genes in the human genome. This targeted sequence, also referred to as a medical exome, sequences the coding regions of these 5,000 genes, providing in one test a vast

trove of personalized knowledge that can aid in both diagnosis and counseling. "This test concentrates on a battery of genes and coding regions of genes that clinicians have sufficient knowledge about, such that if something out of the ordinary is found they can investigate further," says Mr. Smith. The reason for only sequencing a portion of the genes with this test is that while an individual's entire genome can be sequenced, all 3 billion base pairs and roughly 19,000 to 20,000 genes, a large portion of this information is simply not understood at present. Therefore, this testing evaluates only those regions of genes for which the science sufficiently exists to allow interpretation and action in some way by the clinician.



Aleksandar Rajkovic, MD, PhD



Dr. Rajkovic and colleagues in the lab.

Mr. Smith explains that this new test will have particular value with the pediatric population as a way to possibly prevent or reduce the diagnostic odyssey for children with complex or multifactorial conditions of known or unknown origin. “Exome testing a child who has eluded diagnosis may help us find the genes or gene pairings that most likely explain the features of the illness. This will allow the clinicians to better understand how to manage and treat the individual, while at the same time reducing or preventing the idea of the diagnostic odyssey — of looking at individual suspected causes one at a time over many months or years,” says Mr. Smith.

Cutting-Edge Research and New Grants

Whole-Exome Sequencing

Dr. Rajkovic and his colleagues are active on numerous research fronts. One exciting area of exploration centers on how to better diagnose genetic disorders prenatally and postnatally. “We are looking at the utilization of cutting-edge technologies, such as whole genome sequencing in both prenatal and postnatal diagnosis. Clinically we are involved in this area, but we are also testing the utility of prenatal genome sequencing,” says Dr. Rajkovic. Because the information uncovered in whole genome sequencing is vast, Dr. Rajkovic and his colleagues are investigating how the information is returned to patients, and how much information related to the developing fetus is or should be shared. Some of their findings are discussed in their 2015 paper, “Prenatal Whole-Exome Sequencing: Parental Attitudes,” which surveyed a cohort of 186 individuals and their

preferences regarding knowing the results of fetal whole-exome sequencing. Among the findings were that 54 percent of individuals were interested in the screening for their fetus, and the majority of individuals would want to know about both treatable and nontreatable conditions uncovered in the screening. “We think that this will be a game changer in terms of helping us diagnose the diseases that individuals have prenatally,” says Dr. Rajkovic.

Searching for Noninvasive Options

Dr. Rajkovic is also studying various ways to noninvasively diagnose genetic disease during pregnancy: “One area that shows promise is our current work at Magee in isolating — noninvasively — fetal cells from maternal blood and from the maternal cervix.” The research team’s hope is to eventually show that these noninvasive tests could replace some of the current invasive diagnostic procedures, such as chorionic villus sampling and amniocentesis.



Ed Smith, MS, MBA

The MED12 Gene and Leiomyoma Formation

In July 2017, Dr. Rajkovic was awarded a new NIH RO1 grant² for a project examining MED12 Mechanisms of Uterine Leiomyoma Formation. Past research³ by Dr. Rajkovic and colleagues at Magee has discovered that one particular gene — MED12 — has a significant responsibility in the formation of leiomyomas, or uterine fibroids. Their research has shown that mutations in the MED12 gene are not inherited but rather are actually seminally acquired by the uterus. Dr. Rajkovic’s research has uncovered that almost 70 percent of uterine fibroids have specific mutations in the MED12 gene. “Our research teams have published a number of papers on

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The Pregnancy Recovery Center *Continued from Page 3*

Addressing High-Risk Health Behaviors and Other Complications

High-risk health behaviors with opioid-dependent women is another category of research that Dr. Krans and her colleagues are actively pursuing. "One startling statistic we know is that within the patient population we see, almost 90 percent of pregnancies are unintended," says Dr. Krans, "and the utilization of long-acting reversible contraceptives (LARC) is quite low, less than 10 percent." Dr. Krans recently finished a study³ designed to offer LARC implants in the immediate postpartum period. Through counseling and discussions after delivery, interested individuals could consent to enroll in the study and receive the contraceptive implant Nexplanon® (manufactured by Merck, which funded the trial) prior to their release from the hospital after delivery. "Fifty percent of the women we discussed the option with ended up getting the implant, and we feel that this was an incredibly successful study," says Dr. Krans. The Nexplanon

cohort will be compared against a control group receiving standard postpartum contraceptive care, and participants will be followed for 12 months postpartum. Total enrollment in the study was 200 individuals.

References and Further Reading

- ¹ Study of Hepatitis C Treatment During Pregnancy (HIP). ClinicalTrials.gov Identifier: NCT02683005.
- ² Sofosbuvir/Velpatasvir in Postpartum Women With Opioid Use Disorder and Chronic Hepatitis C Infection. ClinicalTrials.gov Identifier: NCT03057847.
- ³ Immediate Postpartum Nexplanon Placement in Opioid Dependent Women. ClinicalTrials.gov Identifier: NCT02657148.
- ⁴ Opioid Dependence Treatment Therapies in Pregnancy. ClinicalTrials.gov Identifier: NCT03098407.



Members of the Pregnancy Recovery Center: Front (left to right): Georgia Sarantinoudis; Terri McKenzie, MSW, LSW; Stephanie Bobby, BSN, RN; Ali Boast, BSN, RN, CARN; Stacy Freeman-Pistella, MA, LSW. Back (left to right): Robert Gedekoh, MD; Michael England, MD; Elizabeth Krans, MD, MSc; Patty Genday, MSN, MBA, BN; Traci Day, MSW, LSW; Ashley Sulinski; Monique Jackson.

The Center for Innovative Fetal Intervention Continued from Page 7

and anatomic motor levels at 2 years of age, stratified by mode of delivery and presence or absence of labor. “In our study, we found no significant difference in the children delivered via C-section versus vaginally.” This has obvious implications for the mother and the baby. Avoiding a C-section if possible eliminates those inherent risks with the procedure and the implications for future pregnancies, allows for faster recovery, and affords for immediate mother-baby interaction.

“At Magee, our mission is to take care of women and their babies. Even in those rare cases where there may not be a good outcome, or intervention may not prove beneficial, we still have the capacity to help the mother. We always find a way to help her and the family through difficult times,” says Dr. Emery.

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The Center for Medical Genetics and Genomics Continued from Page 11

the role of MED12 in leiomyoma formation. With our new research into MED12 mutations driving fibroid formation, we theorize that in the future it may be possible to target this gene and its mutations with noninvasive treatment alternatives,” says Dr. Rajkovic.

Ovarian Reserves and Premature Ovarian Insufficiency

Another current grant in progress seeks to understand and use an individual’s genetic profile as a biomarker for ovarian reserves. Understanding one’s reproductive capacity and duration is becoming more important in fertility and infertility as individuals postpone or delay pregnancy. These individuals would like to know whether they should be freezing their eggs, or whether they can wait and reproduce later. Research by Dr. Rajkovic has been using genome sequencing of individuals who experience early loss of fertility — premature ovarian insufficiency — to gain a better understanding of the basic biology and genetic underpinnings responsible for premature ovarian insufficiency.

Past and current research⁴⁻⁷ by Dr. Rajkovic has identified a number of genes that play an important role in premature ovarian insufficiency. The current understanding is that the most important gene related to premature ovarian insufficiency is the MCM8 gene. This gene is involved in DNA damage response. When DNA becomes damaged, either by internal or external environmental factors, the body needs to repair that damage. The MCM8 gene appears to be critical in an individual’s ovarian reserves, and it plays a role in determining a women’s reproductive lifespan, explains Dr. Rajkovic.

References and Further Reading

- Kalynchuk EJ, Althouse A, Parker LS, Saller DN Jr, Rajkovic A. Prenatal Whole-Exome Sequencing: Parental Attitudes. *Prenat Diagn.* 2015; 35(10): 1030-1036.
- MED12 Mechanisms of Uterine Leiomyoma Formation. NIH Award 1R01HD088629-01A1. Primary Investigator: Aleksandar Rajkovic.
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- Magee.UPMC.com
- Obgyn.Pitt.edu
- PittGenomics.org

Welcoming New Faculty

The Department of Obstetrics, Gynecology, and Reproductive Sciences is pleased to welcome two new faculty members to the department, **Ronald Buckanovich, MD, PhD**, and **Lan G. Coffman, MD, PhD**.



Dr. Buckanovich is professor of medicine and a fellowship-trained hematologist-oncologist with previous appointments at the University of Michigan and the Hospital of the University of Pennsylvania. Dr. Buckanovich's research focuses on ovarian cancer biology and the development of novel prevention and therapeutic interventions. Past work by Dr. Buckanovich has involved tumor-associated macrophage studies, as well as molecular profiling of ovarian cancer tumor endothelial cells, defining of a cancer stem cell hierarchy, and identifying a population of carcinoma-associated mesenchymal stem cells and defining their impact on ovarian cancer stem cell proliferation.

Research into aspects of the tumor microenvironment has led to the definition of distinct subpopulations of ovarian cancer cells, all responding differently to different growth factors and with different metastatic and chemotherapy-resistant patterns. In order to target the chemotherapy-resistant population of cells, his group has developed a novel small molecule inhibitor of the ALDH1A family. In order to test novel therapeutics in a more physiologically relevant manner, Dr. Buckanovich and his colleagues developed a novel humanized tumor model to engraft human cancer stem cells in a human tumor microenvironment for testing.

Dr. Buckanovich is currently the primary investigator of several grants from the NIH and U.S. Department of Defense, looking respectively at ovarian cancer cell quiescence and chemotherapy resistance, cancer cell asymmetric division, and a novel, nontoxic ovarian cancer prevention therapy, and to further develop the

humanized tumor stroma animal model. Additional support from the NIH is pending for studies to study and develop an antibody therapy to prevent cancer growth and metastasis.



Dr. Coffman joins the department as an assistant professor of medicine and is also a fellowship-trained hematologist-oncologist previously with the University of Michigan. Dr. Coffman's basic and translational research interests primarily involve ovarian cancer basic biology, the tumor microenvironment, mechanisms of metastasis, and mesenchymal stem cells, and her clinical focus is on the

treatment of gynecologic malignancies.

With regard to the role of the tumor microenvironment in ovarian cancer metastasis, Dr. Coffman is pursuing research into stromal cell promotion of metastasis and the ovary as the initial site of metastasis rather than the site of origin in high-grade serous ovarian cancer.

Additionally, Dr. Coffman is pursuing the role of carcinoma-associated mesenchymal stem cells in tumor growth and chemotherapy resistance, as well as the implications of hypoxia and tumor-infiltrating lymphocytes in the tumor microenvironment. Dr. Coffman's current grant support includes funding from the NIH with an \$800,000 K08 grant to better define the formation and function of carcinoma-associated mesenchymal stem cells in the ovarian cancer microenvironment, and a Tina's Wish Rising Star grant to study targeting carcinoma-associated mesenchymal stem cells to prevent the establishment of the ovarian cancer microenvironment.

Maternal Fetal Medicine at Magee *Continued from Page 5*

to baby during pregnancy. Understanding the risk factors and probability of transmission is critically important to the epidemiology and biology of perinatal HCV transmission, but also to the design, plan, and execution of a treatment trial of nonpregnant individuals. "This study² will allow us to follow women through pregnancy with viral load studies and genotyping, and follow children for two years postpartum to understand the factors during pregnancy and postnatally related to transmission," says Dr. Simhan.

The ARRIVE Study: Induction Versus Expectant Management

With recruitment recently completed, Dr. Simhan and his study³ collaborators are eagerly anticipating the data analysis of a randomized trial of induction of labor versus expectant management at 39 weeks of gestation and uncomplicated pregnancy. "We hypothesize that this study will help us understand how better maternal and newborn outcomes can be realized. This has the potential to really change obstetrical practice into the future," says Dr. Simhan, who indicates that results of the study are expected to be available later this year.

Cytomegalovirus Research

An ongoing trial¹ currently enrolling patients involves the cytomegalovirus (CMV). The most common cause of congenital deafness, it can also cause blindness and affect cognitive development. This study is enrolling women with primary CMV infection in pregnancy and randomly assigning them to receive the CMV hyperimmune globulin or a placebo to examine whether reductions in perinatal transmission of CMV occur.

References and Further Reading

- 1 A Randomized Trial to Prevent Congenital Cytomegalovirus (CMV). ClinicalTrials.gov Identifier: NCT01376778.
- 2 An Observational Study of Hepatitis C Virus in Pregnancy. ClinicalTrials.gov Identifier: NCT01959321.
- 3 A Randomized Trial of Induction Versus Expectant Management (ARRIVE). ClinicalTrials.gov Identifier: NCT01990612.

Detailed information about the Maternal-Fetal Medicine Units Network can be found at MFMU.bsc.gwu.edu.

About the Department

The Department of Obstetrics, Gynecology, and Reproductive Sciences encompasses a full range of specialties and clinical services for patients, as well as a broad research portfolio and accredited subspecialty training programs for physicians.

Patient care is centered at Magee-Womens Hospital of UPMC, home to one of the largest and most respected clinical care programs in the country. Magee-Womens Hospital of UPMC is ranked in the top 12 hospitals for gynecologic care by *U.S. News & World Report*, and is recognized as a National Center of Excellence in Women's Health by the U.S. Department of Health and Human Services. At Magee, more than 10,000 babies are delivered each year, and the hospital currently operates the largest neonatal intensive care unit in Pennsylvania, treating more than 1,500 patients annually.

Divisions and Specialty Women's Health Services

Magee-Womens Hospital of UPMC offers a full spectrum of obstetric, gynecologic, and reproductive health services and specialty programs for patients. These include:

General Obstetrics and Gynecology — Featuring specialty programs and treatments for endometriosis, uterine fibroids, and other common conditions.

Gynecologic Oncology — In collaboration with the UPMC CancerCenter, the gynecologic oncology program provides a comprehensive, multidisciplinary approach to the treatment of gynecologic cancers.

Breast Cancer and Breast Surgery — Magee-Womens Hospital is a national leader in breast cancer research, clinical trials, and patient care for patients with breast cancers and other disorders.

Maternal Fetal Medicine — For complicated pregnancies, the maternal fetal medicine program offers consultation, diagnostic testing, and care management for high-risk pregnancies before, during, and after pregnancy.

Midlife Health Services — Physicians in the Midlife Health Services program specialize in the treatment of the symptoms of menopause, and on those women experiencing premature or perimenopause with accompanying symptoms.

Midwifery — Midwifery services at Magee are comprehensive, from prenatal care through labor and delivery, and are provided by a team of board-certified midwives licensed in both nursing and midwifery.

Minimally Invasive Gynecologic Surgery — With one of the largest contingents of fellowship-trained surgeons on staff, the minimally invasive gynecologic surgery program offers state-of-the-art treatments and procedures for a range of issues that include hysterectomy, ovarian cysts, endometriosis, pelvic pain, and others.

Obstetrical and Gynecological Ultrasound — Women's imaging services at Magee are provided by specially trained, board-certified physicians and staff skilled at various breast imaging and ultrasound-guided biopsies, OB ultrasound, bone density scans, and other diagnostic imaging tests.



Reproductive Endocrinology and Fertility — The Center for Fertility and Reproductive Endocrinology provides patients with onsite access to a full range of diagnostic and treatment programs for infertility issues for both women and men, including in vitro fertilization, fertility preservation, preimplantation genetics, and preconception counseling, among other services and support.

Reproductive Genetics — The Division of Reproductive Genetics and Genomics provides clinical evaluation and genetic counseling to men and women with genetic/genomic disorders, including preconceptional, prenatal, adult, and cancer cases.

Urogynecology and Pelvic Reconstructive Surgery — The Division of Urogynecology specializes in the diagnosis and treatment of a range of conditions that include chronic urinary tract infections, pelvic organ prolapse, urinary incontinence and pelvic pain.

Fellowship Training Programs

The Department of Obstetrics, Gynecology, and Reproductive Sciences currently offers a number of accredited fellowship-training programs for prospective physicians:

- Maternal Fetal Medicine
- Medical Genetics Residency
- Reproductive Endocrinology and Fertility
- Female Pelvic Medicine and Reconstructive Surgery
- Gynecologic Oncology
- Reproductive Infectious Diseases and Immunology
- Minimally Invasive Gynecologic Surgery
- Family Planning

Areas of Research

As the top recipient of NIH-funded research grants for obstetrics and gynecology in the country, researchers at Magee-Womens Hospital and collaborative partners at the Magee-Womens Research Institute are deeply involved in many novel basic, translational, and clinical studies. Primary research areas include:

- Reproductive development
- Pregnancy and newborn medicine
- Infectious diseases
- Gynecology
- Reproductive endocrinology and fertility
- Women's cancer
- Women's health and wellness
- Genetics



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To learn more about the UPMC Department of Obstetrics, Gynecology, and Reproductive Sciences, please visit UPMCPhysicianResources.com/Gynecology.



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