

UPDATES IN GYNECOLOGY

Inside This Edition

- 2** Preserving the Future: Advances in Fertility Preservation, Reproductive Translational Science, and Clinical Programs
- 6** New Findings from the ARRIVE Trial: Induction Versus Expectant Management in Low-Risk Pregnancy
- 8** Reproductive Genetics Division Recruits New Director
- 9** New Leadership at UPMC Magee: Richard Beigi, MD, MSc, Appointed President
- 10** Department News Briefs
UPMC at SMFM 2019
UPMC Physician Resources
- 11** About the Department



Message from the Chairman

Dear Colleagues,

There are many exciting changes occurring in our Department of Obstetrics, Gynecology, and Reproductive Sciences, and also universally at UPMC Magee-Womens Hospital.

To begin with, I would like to welcome **Michael T. Bashford, MD**, to our department as our new director of the Division of Reproductive Genetics. Dr. Bashford comes to UPMC Magee after having a distinguished 30-year career with the U.S. Air Force. Dr. Bashford's expertise in clinical and reproductive genetics, and his experience developing and expanding a large-scale clinical genetics program within the U.S. Department of Defense will no doubt lead to improvements, advances, and expansion of our own programs.

Kyle Orwig, PhD, primary investigator of the Orwig Laboratory, director of research in reproductive endocrinology and infertility, and director of the Fertility Preservation Program in Pittsburgh, shares some of his latest research and groundbreaking clinical trials in fertility preservation. His work to preserve the future fertility options of young children in need of potentially toxic chemotherapy is on the cusp of major breakthroughs and advances. Dr. Orwig's research is extensive, so I invite you to read more about his work in this article and explore those links provided for a deeper understanding of the scope of his work.

Hyagriv Simhan, MD, MS, professor and executive vice chair of obstetrical services, provides a succinct summary of the recently completed ARRIVE study that is already helping to reshape clinical practice in the world of obstetrics.

Finally, I would like to congratulate **Richard Beigi, MD, MSc**, on his recent appointment as president of UPMC Magee-Womens Hospital.

Robert P. Edwards, MD

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

Preserving the Future: Advances in Fertility Preservation, Reproductive Translational Science, and Clinical Programs



Kyle Orwig, PhD, is a professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences with secondary appointments in microbiology 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 of UPMC (FertilityPreservationPittsburgh.org).

Broadly speaking, Dr. Orwig's various basic and translational science studies and his clinical applications of new technologies are all designed to help the significant numbers of individuals in the United States (approximately one in seven couples) with some form of fertility or reproductive deficit overcome their infertility, or preserve their future reproductive abilities when faced with illnesses and treatments that could compromise their ability to conceive a child.

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 this article, Dr. Orwig discusses many aspects of the basic science and translational programs he and his colleagues are currently engaged in, new technologies and pilot studies soon to be underway in human trials, cutting-edge therapies and clinical programs to preserve fertility options for childhood cancer survivors, and the unique capabilities that exist at UPMC and UPMC Magee-Womens Hospital to preserve, protect, or augment an individual's fertility options using novel approaches built on decades of groundbreaking research and clinical expertise.

A Comprehensive Approach to Fertility Preservation and Research

UPMC Magee is a rare institution in the field of reproductive science and infertility research. There are few places in the country that have the ability to translate bench discoveries into clinical practice in ways that are happening at UPMC.

"Regardless of your research discipline, the relevant patients are being seen in UPMC clinics from across the street, next door, or down the hall. Patients travel from across the country and around the world to access pioneering medical care developed in research laboratories at the University of Pittsburgh and translated to the clinics of UPMC. This capability does not exist in very many hospital systems or research institutes in this country. It is never easy to translate findings from the bench to the clinic, but here it is eminently possible," says Dr. Orwig.

One characteristic of UPMC Magee is that it exists as part of a rarified group in the United States that has the ability to provide fertility preservation options for men, women, boys, and girls — at virtually all ages — from neonates to adults.

The Fertility Preservation Program in Pittsburgh

A collaboration between colleagues at the UPMC Magee Center for Fertility and Reproductive Endocrinology, UPMC Children's Hospital of Pittsburgh's divisions of Pediatric Oncology and Urology, and the Orwig Laboratory has established the Fertility Preservation Program in Pittsburgh.

This Program is a multidisciplinary effort to educate patients and physicians about the reproductive consequences of diseases and medical treatments, provide access to established fertility preservation options, and develop new reproductive technologies for patients who currently have no options to preserve their fertility.

The Program currently has experimental protocols to freeze testicular tissue for men and boys who are not able to preserve a semen sample before initiating surgery or medical treatments that may compromise their fertility. The Program is also freezing ovarian tissue for women and girls who are not able to freeze eggs or embryos, as well as freezing eggs for women who are not able or do not desire to freeze embryos. Egg freezing transitioned from experimental to standard of care in 2010 and it is expected that ovarian tissue freezing will transition to standard of care

later this year. Additionally, research being conducted through the Program is evaluating the effects of chemotherapy on sperm to help accurately counsel men about whether their treatment will increase their risk of having children with birth defects.

The Fertility Preservation Program provides world-class fertility care services for adults and children. For individuals receiving cancer treatment or getting ready to deploy with the armed forces, the Program can give them options to begin or add to their family.

The Program allows adult men and women to freeze eggs, sperm, or embryos prior to cancer treatment, prior to transgender treatments, or prior to deployment to the armed services. There are no standard options to preserve the fertility of boys and girls who are not yet producing mature eggs or sperm. For these young patients, we are approved to freeze testicular tissue or ovarian tissue that might be used in the future to restore fertility when experimental techniques emerge from the research pipeline.

To learn more, please visit FertilityPreservationPittsburgh.org.

“This ability is quite valuable to us because the spectrum of patients we are able to treat or offer experimental research protocols to informs our practice and educates us faster than if we were more specialized or focused on a single kind of research, technology, or patient population,” says Dr. Orwig.

Moreover, the fertility preservation programs at UPMC are pioneers in preserving testicular and ovarian tissue for children — specifically, those children with a clinical cancer diagnosis whose chemotherapy or radiation treatments put them at a significant risk for future infertility as a consequence of gonadotoxic therapies (see below for more information on these programs and research protocols).

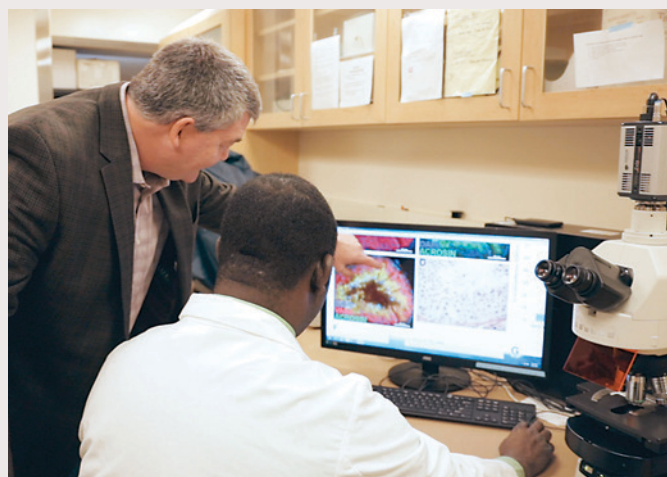
“Most health care systems do not have dedicated and diverse hospitals like UPMC Children’s, UPMC Hillman Cancer Center, and UPMC Magee as part of their network. Furthermore, most stand-alone children’s hospitals do not have the infrastructure, expertise, or wherewithal to engage reproductive medicine and the basic and translational science that is necessary to provide fertility preservation care to children. However, at UPMC, we have adult hospitals, a children’s hospital, a national cancer research center, and female and male fertility care centers all under a single umbrella. This fosters close collaboration and truly multidisciplinary research and clinical care. When you pair the diverse clinical infrastructure with the incredibly robust basic and translational science programs at work at UPMC, it makes for an exciting and productive place to practice and study,” says Dr. Orwig

Fertility Preservation for Children With a Cancer Diagnosis

A relatively common consequence of chemotherapy and radiation treatments for various cancers is permanent infertility through exposure to chemotherapy or radiation. This is true in both adults and children, but it is particularly important for children because the survival rates for most childhood cancers now exceed 85 percent or more as a result of the steady improvements in treatment options over many decades.

The treatments for childhood cancers are effective against the malignancy but can have lasting toxic side effects on other tissues such as the ovaries or testes.

“With high survival rates for pediatric cancer patients, we are seeing a surge in survivors who still have their entire reproductive lives in front of them. These children, some of whom are only one or two years old, lack the maturity to think about and value their family planning options 20 or 30 years into the future. Our program helps families, in a very compressed timeframe between diagnosis and the start of treatment, weigh the options and develop a plan. Part of our mission is to be good communicators with families and physicians to advise on the fertility risk of their cancer treatments and the options to preserve fertility we can currently provide. This must occur rapidly because time is of the essence in treating their cancer. It requires tremendous coordination behind the scenes and it involves building relationships not only throughout UPMC but nationwide because we treat individuals from across the United States and around the world,” says Dr. Orwig.



For prepubescent boys and girls, Dr. Orwig and his program have several approved experimental protocols to preserve testicular and ovarian tissue samples for child candidates that meet the criteria for being at significant risk of future infertility due to their medical treatment. Dr. Orwig and his team share these protocols broadly and are currently enrolling patients through nine coordinated centers in the United States and two in the Middle East.

Through surgical procedures conducted by colleagues at UPMC Children’s and UPMC Magee, testicular tissue and ovarian tissue is secured and cryopreserved for the possible restoration of fertility in the future when experimental techniques emerge from the research pipeline — techniques that Dr. Orwig and his collaborators are now studying to develop and test their safety and efficacy.

“There is an important benefit of our fertility preservation work with these young cancer patients and their families that is outside of the direct fertility focus of the program; and that is the psychological and emotional benefit of planning for a productive and fertile life after cure starting from the moment of diagnosis,” says Dr. Orwig. “It may be years or decades before we can successfully restore these individuals’ fertility using their preserved tissues, but there is potential and this is a positive benefit for families. In the laboratory, we are committed to developing the next generation of reproductive technologies that will allow patients to use their tissues in the future. Several of those technologies are supported by years of safety and feasibility testing across multiple animal models and set to enter the human trial phase in the near future.

Restoring Fertility — Ongoing Trials and New Technologies on the Horizon

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 babies have been produced from cryopreserved testicular tissues, but Dr. Orwig’s team is working hard to address that problem.

Continued on Page 4

Fertility Preservation *Continued from Page 3*



“We’ve been freezing tissues for these patients for almost a decade now and will soon be able to start trials to begin the process of restoring fertility,” says Dr. Orwig.

Spermatogonial Stem Cells and Reimplantation Technologies

Dr. Orwig’s laboratory has extensive expertise in transplanting spermatogonial stem cells back into the testes of animal models to regenerate sperm production in the normal manner.

“We’ve demonstrated that we can do this successfully and safely in mice and rats and monkeys, and we think that it is a technology that’s ready to go to the clinic. It’s an extraordinarily robust technology, it is 25 years old, being first described in 1994, and has been replicated in numerous animal species. It works. Our team members are technical experts at implanting those stem cells in order to regenerate spermatogenesis. It is a mature technology and we are in the process now of teaching urologists around the country how to implement the technology so that they can transplant stem cells back into patients,” says Dr. Orwig.

For transplanting spermatogonial stem cells back into pediatric patients, Dr. Orwig and his colleagues are working on preliminary experiments in adult patients in order to obtain the necessary safety and efficacy data to gain IRB approval to perform the procedures on their pediatric candidates.

“We have outlined a path to demonstrate safety and feasibility in five adult patients, which will provide the necessary information for regulatory approval to develop a safe and effective child protocol,” says Dr. Orwig.

Driving Spermatogenesis Outside the Testes

Another technique for restoring spermatogenesis involves implanting intact pieces of testicular tissue somewhere in the body that is outside the testes, such as in the scrotum next to the testes, or subcutaneously anywhere on the body. This approach would bypass the need to isolate the spermatogonial stem cells from the preserved testicular tissue.

“As the individual goes through puberty, it will drive spermatogenesis from the grafted tissue, which at some point could be retrieved along with the sperm produced, that can be used in the IVF clinic to produce a biological child. This is a fairly mature technology with the first experiments done circa 2000,” says Dr. Orwig. “Testicular tissue grafting has been replicated in numerous animal species and we recently produced a healthy monkey baby using this approach.”

While the technique has yet to make it to human trials, Dr. Orwig’s work may make that possible in the near future.

Producing Sperm Outside the Human Body

Imagine a scenario whereby a child leukemia patient with leukemic cells spread all over his body has a testicular biopsy taken and tissue harvested for preservation before being treated for the cancer. In this scenario, it is reasonable to expect that the biopsy might be contaminated with cancer cells. Implanting the spermatogonial stem cells or the intact testicular tissue back into the body might not be safe. One could conceivably reintroduce cancer into a patient that had been effectively cured. Dr. Orwig and his colleagues are extremely cognizant and wary of this possibility.

“Because of this type of scenario, we are thinking about technologies that could produce sperm outside of the body and can include using an animal model. The question that arises with this approach is one related to introducing xenobiotics from the animal. However, we already use certain animal products, particularly from pigs and cows, in human medicine, so there may be a pathway forward with this approach,” says Dr. Orwig. “Testicular tissue xenografting has produced live offspring in mice, pigs, and monkeys.”





Orwig Laboratory staff members.

The other extracorporeal method for sperm generation may reside in a culture dish, according to Dr. Orwig. This method would be a workaround to the animal model concerns, but the technology is highly experimental and only in its infancy.

“This research has only ever been done in a mouse by a single laboratory in Japan. My lab is now trying to replicate this research, not only to show we can reproduce the results here, but to translate them to primates — and ultimately humans — in the clinic,” says Dr. Orwig.

Technologies Not Yet Ready for Primetime

For a technology that may apply to both males and females, Dr. Orwig indicates that it may be possible in the far future to obtain a skin biopsy from a patient and transform the skin cells into eggs or sperm.

“On its face, this may sound like a plot from a science fiction story. However, when done to male and female mice, the procedure has led to the production of live born babies. The methodology is called in vitro germ cells — one of the most cutting edge approaches being studied in the field — and it is very exciting,” says Dr. Orwig.

The problem with this kind of work, in the short term, according to Dr. Orwig, is that once the mouse results come out, everybody wants to jump immediately to human studies.

“We need to conduct systematic studies, first to demonstrate that the initial reports actually can be reproduced by other laboratories — even in mice — but then to translate them to other species to demonstrate safety and feasibility before the clinic. Now, if this approach were to someday make it to the clinic, there won’t be a need to preserve tissue before a child or an adult has therapy to treat cancer. They can just make a decision when they are ready to start a family to have a skin biopsy taken to produce sperm or eggs, as the case may be. I think we’ll be there one day — not anytime soon but there are many dedicated and brilliant researchers working on this and other technologies we previously mentioned,” says Dr. Orwig.

Further Reading

Hermann BP, Sukhwani M, Winkler F, Pascarella JN, Peters KA, Sheng Y, Valli H, Rodriguez M, Esselarab M, Dargo G, Peterson K, Masterson K, Ramsey C, Ward T, Lienesch M, Volk A, Cooper DK, Thomson AW, Kiss JE, Penedo MT, Schatten GP, Mitalipov S, Orwig KE. Spermatogonial Stem Cell Transplantation Into Rhesus Testes Regenerates Spermatogenesis Producing Functional Sperm. *Cell Stem Cell*. 2012 (**Featured article**); 11(5): 715-726.

Dovey SL, Valli H, Hermann BP, Sukhwani M, Donohue J, Castro CA, Chu T, Sanfilippo JS, Orwig KE. Eliminating Malignant Contamination From Therapeutic Human Spermatogonial Stem Cells. *J Clin Invest*. 2013; 123(4): 1833-1843.

Gassei K and Orwig KE. Experimental Methods to Preserve Male Fertility and Treat Male Factor Infertility. *Fertil and Steril*. 2016; 105(2): 256-266.

Clark AT, Gkoutela S, Chen D, Liu W, Sosa E, Sukhwani M, Hennebold JD, Orwig KE. Primate Primordial Germ Cells Acquire Transplantation Potential by Carnegie Stage 23. *Stem Cell Reports*. 2017; 9(1): 329-341. PMID: 28579394.

Jakus AE, Laronda MM, Rashedi AS, Robinson CM, Lee C, Jordan SW, Orwig KE, Woodruff TK, Shah RN. Tissue Papers from Organ-Specific Decellularized Extracellular Matrices. *Adv Funct Mater*. 2017; 27(3): pii: 1700992. doi: 10.1002/adfm.201700992. Epub 2017 Aug 7.

Murdock MH, David S, Swinehart IT, Reing JE, Tran K, Gassei K, Orwig KE, Badylak SF. Human Testis Extracellular Matrix Enhances Human Spermatogonial Stem Cell Survival In Vitro. *Tissue Eng Part A*. 2018; doi: 10.1089/ten.TEA.2018.0147.

Fayomi A, Peters K, Sukhwani M, Valli-Pulaski H, Shetty G, Meistrich M, Houser L, Robertson N, Roberts V, Ramsey C, Hanna C, Hennebold J, Dobrinski I, Orwig KE. Autologous Grafting of Cryopreserved Prepubertal Rhesus Testis Produces Sperm and Offspring. *Science*. 2019; 363(6433): In Press.

Selection of Current Grant Support for which Dr. Orwig serves as the principal investigator:

NIH/NICHD T32 HD087194

Reproductive Development From Gonads to Fetuses

NIH/NICHD R01 HD092084

Improving Fertility Preservation in Boys With Cancer

NIH/NICHD R01 HD076412

Cellular Mechanisms of Chemotherapy-Induced Male Infertility: Stem Cell or Niche?

NIH/NICHD P01 HD075795

Preserving Male Fertility After Cancer Therapy

OrwigLab.org

FertilityPreservationPittsburgh.org

New Findings from the ARRIVE Trial: Induction Versus Expectant Management in Low-Risk Pregnancy



Published in *The New England Journal of Medicine* in August 2018, findings from the national, multicenter “A Randomized Trial of Induction Versus Expectant Management” (ARRIVE) study shed new light on outcomes for low-risk pregnancies in nulliparous women. The trial was sponsored by and conducted through the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.

The trial, conducted between 2014 and 2018, enrolled participants at 41 sites across the United States with slightly more than 6,000 women taking part. The trial was designed to assess whether elective induction of labor in the study cohort — at 39-weeks gestational age — improved neonatal and maternal outcomes compared to expectant management.

UPMC Magee-Womens Hospital was one of the trial sites, and **Hyagriv Simhan, MD, MS**, professor and executive vice chair of obstetrical services, served as the site principal investigator of the study.

Dr. Simhan discusses key findings of the study and its likely influence on clinical practice for this group of low-risk, first-time pregnancies.

Q: Why was this trial needed and what questions was it designed to answer?

A: In essence, prior to this large study, the data we had available and used to guide practice with this group of women was observational only and could not in a definitive way answer the question of which strategy is superior for moms and babies, and which produces better outcomes. This trial was large enough to allow us to detect differences in neonatal outcomes, which was the primary outcome measure — a composite perinatal outcome assessing neonatal morbidity and perinatal mortality on 11 criteria — but it also was able to detect variances in Cesarean section (or C-section) rates and some of the numerous secondary outcomes measures we were interested in and that have significant bearing upon the health of the mother and baby.

Q: Would you highlight any important inclusion/exclusion criteria for this study?

A: The study excluded women who had a medical or obstetrical indication for delivery. For example, diabetes or high blood pressure, or a medical or a fetal issue that would make it unethical to randomize the participant. However, we included women who were obese, of an older age, and from across a range of other demographics, such as socioeconomic status and race. We only excluded women who had prior deliveries of any kind and those who had a medical or obstetrical indication contraindicating a vaginal birth.

Q: What did the study find? Was induction better or worse for mother and baby in this group?

A: Elective induction in this group of women did not portend worse outcomes to either mother or baby compared to the expectant management group. The findings in both approaches were similar.

However, within the elective induction group, we saw a statistically significant lower rate of delivery via Cesarean section than in the expectantly managed group.

- We also saw a significant difference in hypertensive disorders between the two groups, with lower rates in the induction group, and we saw a lower rate of the need for neonatal respiratory support measures among women randomized to induction, showing at least for these three metrics superiority in the induction cohort.

Q: Can you speak to the significance of the lower rates of C-section between the two groups?

A: It is common obstetrical practice in the United States to offer elective induction of labor for women who have had a prior vaginal birth. If the cervix is favorable, elective induction of labor is not known to increase the risk of Cesarean among these women. The unanswered questions remain for women who have had babies before and have an unfavorable cervix and for women who have never had a baby.

For this study, we chose to focus on nulliparous women because it is that group in whom Cesarean section across the board is more common. There are important efforts ongoing to prevent the first Cesarean because it is the best way to prevent their recurrence in the future. The group of women in our study are traditionally at highest risk of a Cesarean because they had never given birth.

We demonstrated a reduced need for Cesarean in the induction group, and that is a positive finding. However, we want to make sure that a reduction of Cesarean risk is not accompanied by an increase in other risks to the mother or baby. That is why I think studying them both together was the right approach. We would not want to demonstrate a reduction of Cesarean but fail to detect harms to a baby. This is the importance of considering them together in a trial of this size. Avoidance of Cesarean section has benefit to the individual woman, society, health care system, and economy at large. It is major abdominal surgery carrying with it well-known and significant risks and potential complications. One of the biggest risk factors for Cesarean in future pregnancies is a C-section in a first pregnancy. With each successive C-section, the risks to the mother compound. It is a benefit to avoiding a C-section that is actually amplified over time. This is why the safe avoidance of a first Cesarean section is an important goal.

Let me be very clear when I say that the C-section is an incredibly effective tool that has saved thousands, if not millions, of women and their babies. However, we want to do only the ones that are absolutely necessary.

Q: Beyond the concrete findings from the study, what else should clinical providers take away from the report?

A: Two things, really, and these are called out specifically by the American College of Obstetricians and Gynecologists (ACOG) in their guidance that was filed at the same time as the publication of the study results. The data from the study are such that elective induction of labor and the risk to the patient ought to be discussed during pregnancy. The decision of whether a particular woman will or will not proceed with induction of labor ought to take place as part of a shared decision-making process that is informed by a patient's preferences for birth while being cognizant of the potential merits of induction. It might be that an individual will choose expectant management given their preference, but they should make this decision in light of the information in our study. This is a preference-sensitive decision; a patient's preferences are critically important. Elective induction of labor is a reasonable choice given the merits demonstrated in the study.

The second point I would like to emphasize is that the conclusions from ARRIVE should only apply to women who would have met the study's inclusion criteria. We should not extrapolate the results to other groups of women, for example, those who have had prior births and women who have risk factors that would have excluded them from participation. We should refrain from indication creep. Both of these points are highlighted in the national guidance.

Q: What has been the response to the study from clinical providers since its publication and that of the contemporaneous practice bulletins from ACOG?

A: Generally favorable. We have not experienced any large outcry or pushback against the study's findings and our collective recommendations. One question that we do see cropping up is, essentially: Are the findings generalizable to where most births happen in the United States? That is to say outside of large, academic centers and in community hospitals. The answer to that question is, yes, the results are generalizable. The reason is simply that



we recruited participants not only from the academic centers participating in the trial but also at affiliated community hospitals. Many of the hospitals in this study did a relatively lower volume of births; many hospitals were not academic in the sense that they didn't have residents, and many of the births were attended by midwives, too. This study is more representative of a general obstetrical population than one otherwise might think.

Q: How else might this study influence clinical practice in the future?

A: One thing we were mindful of in the final report and recommendations was not to mandate a specific method of labor induction. What we advocate for in the article, and what ACOG advocates in their assessment of the study, is that with these inductions, as with any inductions, providers follow evidence of good clinical practice with respect to how induction of labor is handled. This is an important principle to stress. What I see as a side benefit of this study is its potential to force a level of scrutiny on induction practices in general, to ensure that health care systems and providers follow good clinical guidance and practice with respect to how labor is induced — not just in the group of women we specifically studied, but all women who are pregnant and for whom the need may be justified.

Q: Are there any follow-up analyses planned from the ARRIVE trial?

A: The trial group is working on a planned analysis of the resource utilization implications of induction versus expectant management. This is forthcoming and will be important concerning how society, health care systems, and insurance providers see this work from a cost perspective.

References and Further Reading

Grobman WA, Rice MM, Reddy UM, Tita ATN, Silver RM, Mallett G, Hill K, Thom EA, El-Sayed YY, Perez-Delboy A, Rouse DJ, Saade GR, Boggess KA, Chauhan SP, Iams JD, Chien EK, Casey BM, Gibbs RS, Srinivas SK, Swamy GK, Simhan HN, Macones GA; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *N Engl J Med*. 2018 Aug 9; 379(6): 513-523.

A Randomized Trial of Induction Versus Expectant Management (ARRIVE). [ClinicalTrials.gov Identifier: NCT01990612](https://clinicaltrials.gov/ct2/show/study/NCT01990612).

Practice Advisory: Clinical Guidance for Integration of the Findings of The ARRIVE Trial: Labor Induction Versus Expectant Management in Low-Risk Nulliparous Women. The American College of Obstetricians and Gynecologists. Released August 8, 2018. Full text available at [ACOG.org](https://www.acog.org).

Reproductive Genetics Division Recruits New Director



In November 2018, **Michael T. Bashford, MD**, joined the Department of Obstetrics, Gynecology, and Reproductive Sciences as the new director of the Division of Reproductive Genetics. Dr. Bashford also holds the position of chief of clinical genomics and medical director of the Clinical Genomics Laboratory.

Dr. Bashford completed his medical school training at Columbia University College of Physicians and Surgeons in New York City, followed by residencies in obstetrics and gynecology at the United States Air Force Medical Center, Wright-Patterson Air Force Base, and the Naval Medical Center in Portsmouth, Virginia. After a posting as chief of obstetrics and gynecology at Spangdahlem Air Force Base in Germany, Dr. Bashford completed a fellowship in clinical and molecular genetics at the Baylor College of Medicine in Houston, Texas, in 2001.

Prior to joining the Department and UPMC Magee, Dr. Bashford had a distinguished, 29-year career in the U.S. Air Force, attaining the rank of colonel. Prior to his retirement, Dr. Bashford was stationed at Keesler Air Force Base (AFB) in Biloxi, Mississippi, where he practiced and held several positions of leadership, the most recent of which was director of the Air Force Medical Genetics Center and Laboratory, a position he held for nearly 20 years. The genetics center at Keesler AFB is the only genetics center and laboratory for the entire U.S. Department of Defense and routinely was responsible for more than 30,000 laboratory screenings at the time of Dr. Bashford's departure in 2018.

During his Air Force career, Dr. Bashford obtained significant administrative experience in the field of clinical genetics, as well as in health care management and insurance programs. He served on medical review panels and genetic testing review committees for TRICARE, the health care program for uniformed service members, retirees, and their family members, that is managed by the Defense Health Agency.

His work directing the genetics center and laboratory at Keesler AFB saw the laboratory become the reference lab for the entire Department of Defense. He oversaw the evolution and construction of a testing network between facilities, leveraging the electronic medical records and allowing for seamless ordering and conduction of genetic testing. Dr. Bashford also was working on a pilot program prior to his retirement to educate primary care providers on genetics and genetics testing, an initiative that he indicates will be one of his priorities at UPMC.

"The world of genetics may be the most rapidly changing field in all of medicine. The capabilities and testing platforms that we are using now have only been available in the last five years. There is also a significant dearth of genetic counselors and geneticists that are needed to fill the exploding growth and needs of the medical community. This poses considerable challenges to physicians and systems in how to ascertain, use, interpret what tests are available, when they are and are not necessary, what the results mean, and how those results may be actionable. These are some of the problems I'll be working on within the Department, and also more broadly across the UPMC system and for the UPMC Health Plan," says Dr. Bashford.

Department and Systemwide Priorities

Dr. Bashford's experience managing a large Air Force genetics lab and network of facilities will prove to be a benefit for the large, integrated delivery and finance system UPMC has become. There are several areas of emphasis he will be working on, both short- and long-term.

With genetic testing services and capabilities, there is a systemic desire at UPMC to grow and evolve the laboratory network to offer more services to greater numbers of patients in need.

"Adding testing capabilities, expanding the size of existing labs, and extending our reach into outlying communities through such things as tele-genetics platforms are among my priorities within a Department that has much experience and success with providing a seamless network of care and services across the UPMC system as it does with its maternal fetal medicine and ultrasound programs," says Dr. Bashford.

Dr. Bashford's prior work with TRICARE while in the Air Force will prove valuable in initiatives and collaborations with the UPMC Health Plan. In recent weeks, a genetic testing governance committee was to work on developing standards and policies around molecular genetic testing.

"The ultimate goal is to make sure the right tests are available for the right patients at the right time. Unneeded or unwarranted testing has financial implications, and the speed with which new testing capabilities are being developed requires a concerted effort to remain up to date and knowledgeable enough to inform the decision-making process," say Dr. Bashford. "I think my prior experience doing just that in the Air Force, along with my clinical and molecular testing background, will be put to good use at UPMC."

Another area of focus for Dr. Bashford will be expanding clinical genetic services on the adult side of the care spectrum, an underserved area at present. For many years, if someone needed to see a geneticist it typically involved a baby or a child with birth defects or a confusing undiagnosed condition, or a pregnant mother with a fetal issue.

Now, nothing could be further from the truth. The need for genetic screening and test interpretation has permeated into the world of oncology in order to optimize treatment and surveillance regimens; it has trickled into the spectrum of autoimmune disorders for which the identification of underlying genetic factors may prove valuable; in cardiology where it can impact decisions about prophylaxis for sudden death; and most other areas of health care. As the progression toward more individualized care and precision medicine platforms takes root, the need for genetic testing and counseling resources will continue to grow.

“More adults are having genetic diagnoses made for their conditions and we are working to increase our capabilities to serve this growing population. Collaborations with the Division of Medical Genetics at UPMC Children’s Hospital of Pittsburgh are underway to expand our capabilities with adults. We’re initiating a clinic that will function on a very limited basis for now, but includes plans for expansion in the mid- to long-term,” says Dr. Bashford.

Provider education will continue to be crucial, not only for its own sake, but because primary care clinicians and other specialists will

have to shoulder some of the workload due to the lack of sufficient numbers of geneticists and counselors.

“Primary care doctors will have to increase their knowledge of genetic testing and genetic information, and it is incumbent upon us to develop and implement provider education platforms and tools to provide them the knowledge they can use to discuss genetics with patients, when they should refer to a genetic specialist, what testing can and cannot tell us at present, and how that information (some of which is being brought to them directly by their patients) can be interpreted.”

“It was important to me, and obvious when I interviewed for this position, that there is huge potential at UPMC to blaze a trail into the world of personalized and precision medicine. Bringing together a leading academic institution, a large and expanding health care network, and an integrated insurance plan offers many opportunities for clinicians like myself. It’s an exciting place to be right now, which is why I am here,” says Dr. Bashford.

New Leadership at UPMC Magee: Richard Beigi, MD, MSc, Appointed President

In November 2018, UPMC appointed **Richard Beigi, MD, MSc**, as the new president of UPMC Magee-Womens Hospital. His tenure as president officially began on January 1. Dr. Beigi is the first physician to lead a UPMC hospital.

Dr. Beigi succeeds Leslie Davis, who held positions as Magee’s president and senior vice president, and as executive vice president and chief operating officer of the Health Services Division of UPMC.

“Dr. Beigi has deep compassion for patients, and combined with his intelligence and leadership he is the ideal new president of Magee. I have full confidence that the hospital, supported by an excellent executive team, is in highly capable hands,” says Ms. Davis.

“Dr. Beigi also will bring his commitment to academic rigor and, combined with his compassionate leadership, UPMC Magee will only get better because of him.”

Prior to his appointment as president, Dr. Beigi was UPMC Magee’s chief medical officer, a position in which he worked to ensure that patients receive the highest quality treatment and care from Magee’s medical team.

“It is a true honor and privilege to be appointed president of Magee,” says Dr. Beigi. “I look forward to this responsibility and to building upon UPMC Magee’s strengths in providing best-in-class care to

our patients in all of the communities we serve. I also remain committed to advancing and conducting research that will offer new insights into and answers for how we can best care for our patients.”

His 17-year tenure at UPMC has included positions of increasing responsibility at UPMC Magee and with the University of Pittsburgh School of Medicine.

Throughout his career, Dr. Beigi has remained committed to the academics of medicine, publishing hundreds of peer-reviewed articles, collaborations, abstracts, and studies and teaching tomorrow’s doctors as a professor of reproductive sciences in the Department of Obstetrics, Gynecology, and Reproductive Sciences.



Department News Briefs

Inaugural Magee-Womens Research Summit

October 9 and 10, 2018 saw the inaugural Magee-Womens Research Summit hosted by the Magee-Womens Research Institute in Pittsburgh, Pennsylvania. The summit convened more than 400 innovators in women's health research, community advocates, and leaders from around the world to tackle key issues influenced by the early stages in life. The centerpiece of the summit was the awarding of the first Magee Prize, a \$1 million award for collaborative and transformative research within the reproductive sciences.

The award was presented to an international research team led by **Yaacov Barak, PhD**, associate professor of obstetrics, gynecology, and reproductive sciences at the University of Pittsburgh. Dr. Barak's team includes Myriam Hemberger, PhD, a placenta expert from the

University of Calgary, and Henry Sucof, PhD, of the University of Southern California who specialized in the study of the heart.

The researchers plan to use the prize, which is funded by the Richard King Mellon Foundation, to develop a diverse collection of mouse models which they will use to better understand the placenta-heart connection and the mechanisms that lead to the development of heart defects.

This information may greatly improve early detection and prevention or treatment approaches in the future.

"I have been working on this project and idea for 20 years. It is gratifying to know that persistence pays and yesterday's wild ideas may become today's reality," says Dr. Barak.

UPMC at SMFM 2019

Each winter, the Society for Maternal-Fetal Medicine meets to share the latest innovations and clinical care through education seminars and research presentations. The 39th annual SMFM Pregnancy Meeting was held February 11-16 in Las Vegas. At this year's meeting, UPMC physicians and researchers presented "Subtypes of Gestational Diabetes Mellitus Based on Mechanisms of Hyperglycemia."

Maisa N. Feghali, MD, served as the main speaker for the presentation. Dr. Feghali worked alongside **Jacqueline Atlass, MD**; **Ellen Ribar**; **Steve N. Caritis, MD**; **Hyagriv Simhan, MD, MS**; and **Christina M. Scifres, MD**, in preparing the presentation.

UPMC Physician Resources

For the latest CME courses, videos, news, and events for physicians, visit UPMCPhysicianResources.com.

CME Courses

Preeclampsia and Eclampsia

Presented by Arundhathi Jeyabalan, MD, MS

Headaches in Pregnancy Before, During, and After

Presented by Robert G. Kaniecki, MD

Management of Epilepsy in Pregnancy

Presented by Stephanie Paolini, MD

Select Presentation From the 2018 Obstetrical Neurology Conference

Presented by Jonathan H. Waters, MD

Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians and covering a variety of medical and surgical disciplines.

Urogynecology ERAS Pathways

Halina Zyczynski, MD

Division Director, Urogynecology and Pelvic Reconstructive Surgery

Fibroid Treatment Center at UPMC

Richard Guido, MD

Co-Director, Uterine Fibroid Treatment Center

Minimally Invasive Gynecologic Surgery

Suketu Mansuria, MD

Assistant Director, Minimally Invasive Gynecologic Surgery

Endometriosis

Ted Lee, MD

Director, Minimally Invasive Gynecologic Surgery

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 UPMC Magee-Womens Hospital, home to one of the largest and most respected clinical care programs in the country. UPMC Magee-Womens Hospital is recognized as a National Center of Excellence in Women's Health by the U.S. Department of Health and Human Services. At UPMC 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

UPMC Magee-Womens Hospital 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 Hillman Cancer Center, the gynecologic oncology program provides a comprehensive, multidisciplinary approach to the treatment of gynecologic cancers.

Breast Cancer and Breast Surgery — UPMC 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 UPMC 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 UPMC 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 Preservation and Reproductive Endocrinology provides patients with on-site 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, 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 programs for prospective physicians:

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

Areas of Research

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

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



LIFE CHANGING MEDICINE

200 Lothrop St.
Pittsburgh, PA 15213-2582

A \$19 billion world-renowned health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC provides more than \$900 million a year in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution. The largest nongovernmental employer in Pennsylvania, UPMC integrates 87,000 employees, 40 hospitals, 700 doctors' offices and outpatient sites, and a 3.5 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. As UPMC works in close collaboration with the University of Pittsburgh Schools of the Health Sciences, *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals. UPMC Enterprises functions as the innovation and commercialization arm of UPMC, and UPMC International provides hands-on health care and management services with partners around the world. For more information, go to UPMC.com.

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



Contact the UPMC Department of Obstetrics, Gynecology, and Reproductive Sciences at:

UPMC Magee-Womens Hospital

300 Halket Street
Pittsburgh, PA 15213
412-641-4220

Robert P. Edwards, MD
Chair