CARING FOR PATIENTS SAFELY

DISCOVERING TOMORROW’S CLINICAL INNOVATIONS

PREPARING OUR FUTURE LEADERS
# 2010 MESSAGE FROM THE CHAIR

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## YALE-NEW HAVEN HOSPITAL SERVICES

- OBSTETRICS SERVICE
- GYNECOLOGY SERVICE

## CLINICAL PRACTICES

- MATERNAL-FETAL MEDICINE
- REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY
- GYNECOLOGIC ONCOLOGY
- UROGYNECOLOGY AND RECONSTRUCTIVE PELVIC SURGERY
- FAMILY PLANNING

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- GAMETE BIOLOGY GROUP
- MATERNAL-FETAL SCIENCES GROUP
- CANCER BIOLOGY GROUP
- REPRODUCTIVE PHYSIOLOGY GROUP
- REPRODUCTIVE NEUROSCIENCE GROUP

## EDUCATION

- MEDICAL STUDENT EDUCATION
- RESIDENCY PROGRAM
It is with tremendous pride that we announce that Charles J. Lockwood has been elected to the Institute of Medicine (IOM) of the National Academy of Sciences.

The IOM is the health arm of the National Academy of Sciences, which was chartered under President Abraham Lincoln in 1863. The IOM was established in 1970 by the National Academy of Sciences and is recognized as a national resource for independent, scientifically informed analyses and recommendations on issues related to human health. Those elected to the Institute have made significant contributions to the advancement of medical science, health care and public health, and election is considered one of the highest honors in the health sciences.

Dr. Lockwood received his undergraduate education at Brown University, graduating magna cum laude with distinction in his major of developmental biology. His MD degree was obtained from the University of Pennsylvania. He served his Ob/Gyn residency at the Pennsylvania Hospital and his fellowship in Maternal-Fetal Medicine at Yale. He is the editor-in-chief of Contemporary Ob/Gyn, obstetrical editor of UpToDate, and co-editor of four textbooks including the definitive Maternal-Fetal Medicine reference, Creasy & Resnik’s Maternal-Fetal Medicine, Principles and Practice. He is the author of over 230 original research articles and 110 editorials, as well as countless chapters and abstracts. His H-index, an indicator of the number of times an author’s articles have been cited by other articles, and thus a marker of scientific impact and quality, is one of the highest of any academic Ob/Gyn. He has been funded by the NIH since 1992 and is currently the PI or co-investigator on four NIH grants.

He has served on many national committees including NIH study sections, CDC and FDA committees, and the March of Dimes Scientific Advisory Council on Prematurity. He has served in national leadership roles including president of the Society for Gynecologic Investigation (SGI), the leading international reproductive science society; interim chair of the FDA’s Reproductive Drug Panel, and chair of ACOG’s Obstetric Practice and Bulletin-Review (Obstetrics) Committees. He has been named to the Castle Connolly, New York Magazine and Connecticut Magazine’s lists of best doctors for many years. His leadership and impact on the practice and science of Obstetrics and Gynecology over the past two decades have been virtually unmatched.

Joshua Copel, MD, Vice Chair, Obstetrics
Peter Schwartz, MD, Vice Chair, Gynecology
Edmund Funai, MD, Associate Chair, Clinical Affairs
Richard Hochberg, PhD, Associate Chair, Research and Faculty Development
2010 MESSAGE FROM THE CHAIR

Once again I am very proud to share with you our progress in the Yale Department of Obstetrics, Gynecology and Reproductive Sciences during this past academic year. As you peruse the following pages, you’ll see how our Department continues to distinguish itself across all dimensions of our clinical, educational and research missions. We’ve continued to experience expansion of our reproductive sciences research, despite the tight restrictions on federal research funding for fetal and women’s health. We have developed our resident and medical student training programs into one of the premier sites for training future leaders in women’s health. And we have made significant progress in patient safety and satisfaction while growing clinical volume and revenues (see Figure 1).
As is evident in this report, we have continued to innovate in all major areas of women’s reproductive health. Each of our clinical subspecialty sections continues to grow in volume while embarking on significant and exciting new clinical research projects. Examples of our innovation in clinical research include a new emphasis on robotic radical surgery and new drug development and therapeutic vaccines in Gynecologic...
Oncology, a comprehensive Patient Safety Program in Maternal-Fetal Medicine, a trial of novel devices addressing sexual dysfunction and urinary incontinence for our Urogynecology and Reconstructive Pelvic Surgery patients, and a pilot study of vitamin D therapy to address fertility issues in our patients suffering from polycystic ovarian syndrome in Reproductive Endocrinology and Infertility.

Through a continued focus on teamwork and dedication to safety and customer service, our clinical enterprise regularly receives commendation from the Yale Medical Group for excellence in patient care. Five of our physicians were listed as “top docs” in their specialties in New York Magazine’s 2010 “Best Doctors” issue. The Department’s units have achieved the highest Press-Ganey scores at Yale-New Haven Hospital for the past three years. Our faculty practices have also achieved among the top Press-Ganey scores at the medical school.
All of our research groups have continued to grow their research programs despite the universal challenges in obtaining federal funding. Overall annual sponsored funding has grown to $16.3 million, while total annual NIH funding grew to $9.7 million (see Figure 2). This level of federal funding has kept us among the top few Ob/Gyn departments in the nation. In an environment of historically low pay lines for funding new grants, our growth is a testament to the individual drive and collaborative initiatives of our reproductive biology and physician scientists. Just a few of the important recent discoveries in reproductive health research from our labs include:

- Developing a novel potential therapy for both endometriosis and endometrial cancer, targeting tissue factor expression in abnormal neovascularature (Lockwood and Santin labs).
• Identifying protein misfolding as a primary placental defect in preeclampsia and activation of the RAGE pathway as a cause of brain injury in preterm neonates (Buhimschi lab).

• Isolation of ovarian cancer stem cells and potential targeted therapies (Mor and Huang labs).

• Developing a new treatment strategy for Parkinson’s disease that uses adult human endometrial stem cells to generate dopaminergic neurons (Taylor lab).

• Identification of bisphenols as an endocrine disrupter, leading to both endometrial dysfunction and uterine maldevelopment as well as developmental cognitive impairment (Taylor and Leranth labs).

• Novel mechanisms triggering oocyte apoptosis (Johnson lab).

• Development of new biochemical markers for sperm maturity and function to help assess male fertility (Huszar lab).

• New insights into the pathophysiology of infertility: Through the use of molecular markers HOXA10 and BTEB1, Yale researchers have determined that uterine myomas may exert their detrimental effects by affecting the entire endometrium, not just the areas over the fibroids (Taylor lab).
PREPARING OUR FUTURE LEADERS

Our mission in the area of education is to train the next generation of leaders in women’s health. We begin this process at the high school and college levels and continue it through active mentoring of our junior and mid-level faculty. High school students throughout Connecticut have an opportunity each summer to participate in our NIH-funded Discovery to Cure High School Internship Program, led by Dr. Gil Mor. During their internship, promising students learn laboratory techniques in reproductive sciences, conduct their own research project, and present their results during a student research day conference attended by students and faculty. We sponsor a very popular Yale undergraduate course in Reproductive Biology and offer college students from Yale and other universities substantive research experience in our laboratories, prompting many of them to go on to graduate study in reproductive sciences or to medical school.

Our Director of Medical Student Studies and Ob/Gyn Clerkship Director, Dr. Jessica Illuzzi, has transformed the Ob/Gyn Clerkship into one of Yale’s top-rated clinical rotations by incorporating professional actor teaching associates, simulation, small group learning and debate-style forums on controversial topics in Ob/Gyn into the didactic component of the rotation. Her innovations have garnered Jessica the medical school’s top two teaching awards.
We select talented and accomplished graduates from medical school for our outstanding and highly competitive residency program. Our Program Director, Dr. Julia Shaw, has also introduced many new pedagogic innovations, including a dedicated da Vinci surgical trainer. In addition to promoting clinical and academic excellence, our Ob/Gyn Residency Program requires an original research thesis for graduation as a component of training future leaders in our field. We instill a research orientation by sending the entire PGY-1 resident class each year to the Annual Scientific Meeting of the Society for Gynecologic Investigation. Many of our residents co-author multiple peer-reviewed papers with their faculty mentors during their training.

Over 80% of our graduating chiefs enter the nation’s top fellowship training programs, many of them successfully competing for one of our Yale positions. We have highly competitive ABOG-approved fellowships in Maternal-Fetal Medicine, Gynecologic Oncology, Reproductive Endocrinology and Infertility, and Urogynecology and Reconstructive Pelvic Surgery. Our subspecialty fellows routinely present their research at their respective subspecialty societies’ annual meetings and at the Society for Gynecologic Investigation’s annual meeting, where they are selected to give oral presentations and are honored with awards for best research by a trainee.

We are committed to training programs for reproductive physician-scientists as well. The Department sponsors multiple Robert Wood Johnson Foundation Clinical Scholars, an AAOGF Scholar and three Women’s Reproductive Health Research K12 Scholars.
OBSTETRICS SERVICE

OB Safety Culture and Climate

Following up on our continued patient safety efforts, we sustained improvements in our safety culture and climate. Safety culture is defined as the integration of safety thinking and practices into clinical activities, and safety climate is the quantitative description of the culture. While the major goal of our patient safety initiative has been to improve patient safety, reduce patient injury, and decrease liability losses, the effect on staff perception of quality and safety is also important. We continued to measure staff perceptions of safety and teamwork through the Safety Attitude Questionnaire (SAQ), a standardized and validated questionnaire measuring staff attitudes towards safety and quality in the workplace.

Figure 1

Safety Attitude Questionnaire

Percent in Agreement with Positive Environment

0 10 20 30 40 50 60 70 80 90

OB  Resident  RN


32 41 83 83 36 36 61 61 84 78

Safety  Teamwork
We demonstrated clinically significant increases—according to the SAQ criteria of >20%—in perceptions of teamwork culture, safety culture and job satisfaction from 2004 to 2009. In 2004, at study inception, positive perceptions of safety and teamwork cultures were low among obstetrical providers (non-resident physicians and nurse midwives), residents and nurses (see Figure 1). Clinically significant differences were seen in perception of teamwork culture between OB providers and nurses. Perceptions of both safety and teamwork climate demonstrated clinically and statistically significant improvements over time among all three caregiver domains (p<0.01).

**Cesarean Delivery at YNHH**

The increase in national cesarean delivery rates to as high as 32% in 2007 has received great attention lately and is a major concern of leaders in OB. At Yale, we have observed an increase in our overall cesarean rate over the past five years that has mirrored national trends (see Figure 2). Importantly, the rise is mainly attributed to an increase in repeat cesarean deliveries, as our primary cesarean rate has remained stable over time.

These changes have alerted our OB teams, and awareness of this has created two important responses. For the past three quarters we have observed a decrease in our overall cesarean delivery rate with reductions in both primary and repeat cesarean deliveries (see Figure 2). While no specific measure was instituted to address the cesarean rate, improved attention to oxytocin usage with a refined oxytocin protocol has likely contributed. With our rising national and regional repeat cesarean rate, we are now emerging as a referral center for women with abnormal placentation, namely those with placenta previa, accreta and percreta. In response to these complicated cases and in particular the need to coordinate several teams, we have
engaged a “Complicated Cesarean Delivery” guideline and checklist. This document delineates evidence-based recommendations on the preparation of such cases, including imaging modalities, anemia treatments and delivery planning. The checklist provides a step-by-step guide for scheduling, ancillary support coverage (including Gyn-Oncology, Interventional Radiology, Urology and Vascular Surgery), blood bank services and unit (newborn and critical care) notification.

**GYNECOLOGY SERVICE**

**Inpatient Gynecologic Care at Yale-New Haven Hospital**

Inpatient gynecologic care now takes place on the 14th floor of the new spacious, state-of-the-art Smilow Cancer Center (14 North). This unit boasts single rooms with family sleeping space and a commanding view of the city and surrounding areas, wireless connectivity for patients and staff, ergonomic design and layout, and a fully integrated EMR. Gynecologic Oncology, General Gynecology and Urogynecology services share this space to provide truly comprehensive inpatient gynecologic care.
Surgeries performed by the Gynecology Service have been moved into cutting-edge operative suites in the Smilow building. With the addition of two new da Vinci surgical robots, including a dual-console unit that allows two operators to direct the surgical robotic arms, General Gynecology, Gynecologic Oncology and Urogynecology patients have access to the most advanced surgical techniques available to treat benign gynecologic conditions, gynecologic cancer and disorders of the female pelvic floor. These additional units have allowed for streamlined scheduling of these surgeries, reducing waiting times to under two weeks.

During the past year, over 700 gynecologic robotic surgeries, including hysterectomies, cancer staging procedures, sacro-colpopexies and myomectomies, have been performed at YNHH. With additional faculty members added to both Gynecologic Oncology and Urogynecology, these services continue to expand. While gynecologic patients are undergoing surgery, their family members and friends have access to a waiting area that provides amenities such as complimentary beverages, light snacks, newspapers/magazines, high-speed Internet access and real-time information regarding the patient’s progress and status.

While these new technologies and facilities are critical to improving patient care, we can’t ignore the human element. The nursing and support staff on 14 North consistently scores the highest patient satisfaction results in the institution and among the highest in the country. This staff moved along with the beds, monitors, etc. from the old gynecology unit and is a cohesive and caring group of individuals dedicated to women’s health. Physician assistants, who are available five days per week, supplement the resident team to provide around-the-clock attention for the patients receiving care in this unit. Needless to say, there is always someone nearby when the patient bell rings.
Edmund F. Funai, MD, Associate Chair for Clinical Affairs, Section Chief of Maternal-Fetal Medicine and Chief of Obstetrics at Yale-New Haven Hospital, Professor, Yale School of Medicine
Interests: Perinatal patient safety, long-term consequences of preeclampsia, premature birth

Charles J. Lockwood, MD, MHCM, Anita O’Keeffe Young Professor of Women’s Health and Chair
Interests: Premature birth, thrombosis, recurrent pregnancy loss, health care economics

Joshua A. Copel, MD, Vice Chair of Obstetrics, Director of Ob/Gyn Ultrasound, Professor, Director, Yale Fetal Cardiovascular Center
Interests: Prenatal diagnosis, fetal echocardiography, fetal therapy, chorioic villus sampling

Urania Magriples, MD, Associate Professor, Section of Maternal-Fetal Medicine
Interests: Infectious disease, HIV, innovative models of prenatal care delivery

France Galerneau, MD, Associate Professor, Section of Maternal-Fetal Medicine
Interests: Prenatal diagnosis, medical education

Sonya Abdel-Razeq, MD, Assistant Professor, Section of Maternal-Fetal Medicine and Division of Surgical Critical Care
Interests: Critically ill parturients, septic shock, placenta accreta

Antonette T. Dulay, MD, Assistant Professor, Section of Maternal-Fetal Medicine, SMFM/AACOGF Scholar
Interests: Reproductive immunology, inflammation-associated prematurity

Eric Hodgson, MD, Assistant Professor, Section of Maternal-Fetal Medicine, Robert Wood Johnson Scholar
Interests: Health care access, educational program development and evaluation, leadership development

Christina Han, MD, Fellow, Section of Maternal-Fetal Medicine, WRHR Scholar
Interests: Reproductive immunology, international health, information technology

Erika Werner, MD, Fellow, Section of Maternal-Fetal Medicine
Interests: Labor complications, preterm labor, resident education and cost-benefit analysis

For full bios of our Maternal-Fetal Medicine physicians, please visit
http://medicine.yale.edu/obgyn/mfm/people/index.aspx
OUR PHILOSOPHY AND MISSION

Education and Training

An important mission of the Section is to educate and train Ob/Gyn residents, MFM fellows and Yale medical students, not only as supremely competent clinicians and researchers, but also as future academic leaders. During their time with us, Ob/Gyn residents learn to evaluate and manage women with both low- and high-risk pregnancies and receive additional training in perinatal ultrasound. Resident physicians participate actively in all obstetrical surgical cases and outpatient services, and the MFM faculty members are responsible for a comprehensive series of didactic sessions on pregnancy-related complications.

The three-year MFM Fellowship is designed to train a select group of Ob/Gyn generalists in the management of high-risk pregnancies with specific emphasis on perinatal consultation, genetics, advanced obstetric ultrasound and fetal procedures. The program specifically sets aside 18 months for research to ensure training as a physician-scientist and future academic leader in the field of MFM.

The Section of MFM has recently been reviewed by the American Board of Obstetrics and Gynecology (ABOG). In recognition of our rapid clinical growth, multiple opportunities for teaching and continued academic achievement, our program received approval to expand to three fellows per year. Furthermore, given the success of the Section in training academic physicians, the fellowship has been approved by ABOG for five years.
Clinical Services

The Section of MFM consists of 15 attending physicians and eight fellows, each committed to providing the best possible care for our patients in an environment of respect, compassion and understanding. We use an evidence-based approach to obstetric management to optimize pregnancy outcome for both the mother and the baby while minimizing the number of required procedures. We make every effort to actively involve prospective parents in management decisions, ensuring that they are fully informed about all treatment options, are counseled in their language of choice and have ample opportunity to meet and talk with members of the obstetric anesthesia and NICU teams. When our research offers a new treatment option, our patients are the first to benefit. Highlights of our clinical services include:

- A high-risk pregnancy referral center for over two-thirds of Connecticut. We receive approximately five high-risk pregnancy hospital transfers per week and numerous transfers to our outpatient high-risk practice for consultation or ongoing care.
- A state-of-the-art obstetrical ultrasound service, performing over 47,500 scans per year on patients referred from throughout the world.
- Comprehensive genetic counseling and testing. Our innovative program offers “instant” first trimester results in many cases, thereby minimizing days of anxiety.
- Preconception consultation services for women with significant risk factors for a complicated pregnancy.
- Amniocentesis, chorionic villus sampling (CVS), cordocentesis and other fetal procedures (such as fetal laser surgery for Twin-Twin Transfusion Syndrome) that require specialized training.
- Management of complex diabetes cases before, during and after pregnancy.
- The Yale Women and Children’s Center for Blood Disorders, which manages a large number of women with complex coagulation disorders ranging from antithrombin deficiency to complex antiphospholipid antibody syndrome and supports one fellow per year.
- Comprehensive gynecological ultrasound services for general Ob/Gyn providers and gynecologic oncologists.
Research

The research mission of the MFM Section is to coordinate and conduct high-quality basic science, clinical, epidemiologic and translational research in a safe environment for patients and investigators. The Section uses state-of-the-art technology (Doppler, mass spectrometry, micro-array, functional MRI, recombinant DNA and transgenic animals) to accomplish these goals. Please see our list of publications for an overview of our interests and accomplishments. We are proud to have contributed over 140 publications to the literature during the past two academic years.

ACCOMPLISHMENTS 2009-2010

The Section of MFM continues to enjoy unprecedented academic and clinical growth, and the past year was no exception. Among the highlights:

1. Given the desirable environment to practice within Yale MFM and despite the current shortage of MFM specialists around the country, the Section continues to maintain an impressive cadre of 15 faculty members with unique clinical and academic niches.

2. Continued research excellence: The Section is actively involved in expanding our national research footprint. Original research from the MFM Section was presented at numerous national and international scientific conferences. The Section was among the top five US medical schools in presentations at the 2010 Society for Maternal-Fetal Medicine Annual Scientific Meeting in Chicago. In total, the Section had four oral presentations, one of which won an award for best presentation, and 23 poster presentations. A similarly impressive performance was evident at the 2010 Society for Gynecologic Investigation meeting in Orlando, FL (two oral presentations and 19 poster presentations) and the 2009 International Society for Ultrasound in Obstetrics and Gynecology in Chicago, IL (two oral presentations). To maintain this research advantage, the Section now meets on a regular basis to discuss the latest laboratory...
3. National influence: The Section continues to have faculty in leadership positions in national organizations. Charles Lockwood is a recent Past-President of the Society for Gynecologic Investigation while Joshua Copel is President of the Society for Maternal-Fetal Medicine and immediate Past President of the American Institute for Ultrasound in Medicine (AIUM). In addition, three members of the Section are oral examiners for the American Board of Obstetrics and Gynecology. Furthermore, five members of the Section are recognized by Castle Connolly as the “New York Metro Area’s Top Doctors.”

4. The MFM clinical service continues to grow robustly:
   
a. Ultrasound volume has steadily increased, up over 300% since 2002 with over 47,500 scans performed in 2010.
   
b. The First Trimester Down Syndrome Screening Program continues to expand, with over 320 visits per month.
   
c. The number of diabetes cases managed by the Section increased 90% from 2005 for a total of 285 cases in 2009.
   
d. Total clinical revenue has steadily increased every year, now up 230% since 2002.
1. Continue to provide the highest quality of clinical care to our patients and to serve as the premier site for perinatal referrals in southern Connecticut.

2. Continue to lead national and international perinatal research with a continuing focus on prematurity, preeclampsia and patient safety.

3. Educate future leaders in general obstetrics and gynecology and maternal-fetal medicine who will define the future of obstetrics in the United States.

4. Continue to increase the scope and volume of gynecologic ultrasound by at least 10% and to increase the number of emergency ultrasound services referred from the Emergency Department and general Ob/Gyn practices.

5. Expand our fetal therapy program and offer innovative diagnostic and therapeutic techniques for pregnancies complicated by twin-twin transfusion syndrome as well as congenital or acquired birth abnormalities.
In 2004 the Yale-New Haven Obstetrics leadership embarked on a systematic patient safety initiative to reduce adverse outcomes in our inpatient perinatal services. This multifaceted program involved interventions including outside expert review, protocol standardization, the creation of a Patient Safety Nurse and Patient Safety Committee, and training in team skills and fetal heart rate interpretation. Members of all disciplines working on Labor and Birth (physician obstetricians, midwives, anesthesiologists, nurses and ancillary staff) were involved in this effort.

For the first three years of this project we showed a significant decrease in adverse events (as measured by the Adverse Outcomes Index) and a concomitant improvement in safety climate as assessed by validated safety-attitude surveys, success that has been sustained as of this writing. In February 2008, the Section of Maternal-Fetal Medicine presented this work at an Oral Concurrent Session at the 28th annual meeting of the Society for Maternal-Fetal Medicine, receiving an Award of Research Excellence from the program committee. This work was also recently published in the American Journal of Obstetrics and Gynecology as a featured and “Editor’s Choice” article and can be accessed at http://www.AJOG.org or http://www.ajog.org/article/S0002-9378(09)00092-1/fulltext, even to nonsubscribers.

We continue a trend of decreasing quarterly adverse outcomes in our obstetrical services (Figure 1), and our most recent quarter showed the lowest adverse outcome rate to date. Yale Maternal-Fetal Medicine has become a leader in the obstetrical patient safety movement as other services across the nation attempt to implement similar strategies in their own departments. As the AJOG editors comment, “If you do not have such a strategy in place at your hospital, you may soon be asked ‘Why not?’”

**Figure 1**

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Yale-New Haven Hospital Ob Service Adverse Outcomes Trend 9/04 - 8/09
Original Research Articles: 2009


Original Research Articles: 2010


Review Articles: 2009


**Review Articles: 2010**


**Book Chapters**


REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Hugh Taylor, MD, Section Chief, Professor
Interests: Infertility, reproductive surgery, congenital anomalies, DES exposure, implantation/endometrial receptivity, endometriosis, IVF; recurrent pregnancy loss (first trimester), menopause

Pasquale Patrizio, MD, Director, Yale Fertility Center, Professor
Interests: Infertility (female and male), assisted reproductive techniques (IVF, ICSI, PESA, TESE), reproductive surgery, genetics of infertility, PGD, egg donation and surrogacy, reproductive options for women and men with cancer, oocyte cryopreservation

Aydin Arici, MD, Professor
Interests: Infertility, egg donation, recurrent pregnancy loss (first trimester), congenital anomalies, endometriosis

Emre Seli, MD, Associate Professor, Director, Third Party Reproduction
Interests: Infertility, oocyte donation and surrogacy, reproductive surgery, polycystic ovarian syndrome, reproductive options for women with cancer, endometriosis, IVF

Lubna Pal, MD, Associate Professor, Director PCOS Program
Interests: IVF, infertility, menopause, polycystic ovarian syndrome, hypothalamic and pituitary disorders, obesity-related dysfunction and low bone density

Beth Rrackow, MD, Assistant Professor, Director Pediatric and Adolescent Gynecology
Interests: Pediatric and adolescent gynecology, polycystic ovarian syndrome, pelvic pain, endometriosis, infertility, fibroids, reproductive surgery

Pinar Kodaman, MD, Assistant Professor
Interests: IVF, infertility, polycystic ovarian syndrome, endometriosis, reproductive surgery

Ryan Martin, MD, Assistant Professor
Interests: IVF, infertility, polycystic ovarian syndrome

Gabor Huszar, MD, Director, Male Fertility and Sperm Physiology Laboratory, Senior Research Scientist
Interests: Sperm function tests, sperm structure, donor insemination, sperm cryopreservation (freezing) prior to vasectomy, IVF for oncological treatment

Denny Sakkas, PhD, Director, IVF Lab, Associate Professor
Interests: IVF laboratory, PGD, IVF, ICSI, embryo and blastocyst cryopreservation (freezing)

Dorothy Greenfeld, LCSW, Professor
Interests: Patient education, emotional counseling and support

ADJUNCT FACULTY:
Antoni Duleba, MD
University of California, Davis

Thomas D’Hooghe, MD, PhD
Leuven University, Belgium

For full bios of our Reproductive Endocrinology and Infertility physicians, please visit
http://www.yaleobgyn.org/rei/people/index.aspx
The mission of the Section of Reproductive Endocrinology and Infertility (REI) is to provide specialized care for women and men with a variety of reproductive endocrine disorders and infertility, to accomplish cutting-edge research in reproductive biology, and to educate future physicians and specialists. Our Section is committed to improving patient care through conducting innovative clinical and translational research, and through educating future leaders in our discipline.

**Clinical Services**

Our greatest assets are our patients and our staff. Our caregivers select treatments with the highest long-term cure rate with low associated morbidity based on evidence-based therapeutics and in an environment of respect, compassion and sympathetic concern.

**Education and Training**

Our Section provides a well-rounded program of teaching and clinical activities to enable residents to become well versed in the basic and clinical aspects of Reproductive Medicine. During their six-week rotation, residents are taught how to evaluate women with reproductive problems and to implement appropriate non-surgical and surgical treatments. Residents participate in the Section's surgical cases, postoperative care and didactic sessions, and are encouraged to complete suggested readings. Residents
serve as first assistant in all of the Section’s surgical cases. We believe that the knowledge and surgical skills gained from these activities will allow our residents to evaluate and manage reproductive endocrinology and infertility cases.

The Yale REI Fellowship Program is a three-year educational program designed to provide advanced training to obstetrician-gynecologists. The fellowship is approved by the American Board of Obstetrics and Gynecology. Reproductive endocrinologists at Yale are committed to providing excellent and innovative patient care, while advancing the field and training its future leaders. The three-year fellowship consists of both research and clinical components. The first year is devoted to office-based practice and surgical training. The fellows gain experience in the full range of clinical reproductive endocrine and infertility disorders. The second-year curriculum provides an opportunity for mentored research; the fellows conduct laboratory and/or clinical research and enhance their understanding of the latest scientific principles. This training provides comprehensive research opportunities as well as extensive interaction with other scientists. The third year is spent learning the full spectrum of assisted reproductive technologies. Upon completion of the fellowship program, our physicians are expected to become independent leaders in the practice and advancement of the specialty.

Research

The world-class investigators in our Section have advanced our understanding of the cellular and molecular aspects of reproduction and have formulated new or improved diagnostic methods and treatments through their research. At present, the focus of the Section’s research includes gamete biology (sperm, oocyte and embryo physiology), uterine biology (endometrial and myometrial physiology and pathology), ovarian dysfunction, stem cells and menopause. Together with the Reproductive Physiology and Gamete Biology Groups, our Section has initiated multiple translational research projects with direct clinical implications. These projects are expected to improve oocyte cryopreservation techniques, advance our understanding of sperm and oocyte function, increase IVF pregnancy rates, and clarify the adverse effect of adenomyosis, endometriosis and fibroids in fertility. Treatments such as vitamin D supplementation, novel hormone therapy for menopause, several novel treatments for endometriosis, new methods of embryo evaluation and selection, and ovary/oocyte freezing are currently under study.
1. We experienced growth of over 4% in total clinical volume.

2. We have improved our IVF cycle success rates, and for two of the four age categories (<35 and 35-37 years) our live birth rate per transfer was the highest in Connecticut. For donor oocyte cycles, the live birth rate was over 65%.

3. We expanded our Oocyte Cryopreservation Program established three years ago (under HIC approval) for:
   a. Oncology patients wishing to preserve fertility before undergoing chemo/radiotherapy
   b. Patients who for personal reasons do not wish to freeze embryos when undergoing *in vitro* fertilization treatment
   c. Women who do not have a partner and wish to preserve their future reproductive potential
4. We recruited two new faculty members, Drs. Ryan Martin and adjunct faculty D. Thomas D’Hooghe. Dr. Martin heads our Clinical Outreach Program. Dr. D’Hooghe is a distinguished scholar who is a leader in the field of endometriosis research.

5. Yale REI continues its active association with the NIH Reproductive Medicine Network (RMN). In collaboration with Dr. Heping Zhang of the School of Epidemiology and Public Health, we have been designated the data coordinating center for the RMN, the largest organization conducting clinical trials in our field.

6. We maintained our high level of NIH funding and expanded funding from other sources.

7. We have completed plans to open two new offices, one in neighboring Guilford and one in Fairfield County.

GOALS 2010-2011

1. Increase the number of IVF cycles by 10%.

2. Increase growth in overall clinical volume by 15%.

3. Increase third party reproduction (oocyte donation and gestational surrogacy) cycles by 15%.

4. Grow the Egg Freezing Program by 20%.

5. Create a new Egg Donor Bank service.

6. Expand the newly established Ovarian Tissue Cryopreservation Program for oncology patients. This new addition will complete the range of services available to any cancer patients wishing to preserve future fertility.

7. Increase male infertility visits and surgeries by 10%.
Histologic evaluation of the endometrium has been unsuccessful in differentiating fertile from infertile women or detecting differences in endometrial receptivity. With that in mind, a Yale research team has begun to look at important molecular markers for endometrial receptivity and has recently identified genetic differences between women with submucosal uterine myomas and those with normal uteri—differences that likely affect a woman’s reproductive potential. Their research suggests that submucosal myomas affect the entire endometrial lining, not just the endometrium adjacent to the myomas.

To reach that conclusion, the investigators measured several biomarkers that regulate the degree of endometrial receptivity to an embryo. Among the markers they measured was HOXA10, a transcription factor involved in embryonic uterine development and adult endometrial development during each menstrual cycle. They also measured the expression of HOXA11, a protein that likely plays a role in endometrial development and implantation; BTEB1 (basic transcriptional element binding protein), which researchers believe may be involved in endometrial cell growth, and LIF (leukemia inhibitory factor), which may play a role in embryo-endometrial interaction and blastocyst implantation.

Drs. Rackow and Taylor found that HOXA10 was significantly decreased in the endometria overlying the submucosal myoma as well as in the endometria remote from the submucosal myoma. Women without myomas demonstrated comparatively higher levels of gene expression than those who did not suffer from myomas and did not have lower HOXA levels in either the tissue above the growths or in remote areas of the myometrium.

Similarly, the endometria from uteri with submucosal myomas demonstrated a downward trend in BTEB1 mRNA expression, but not in LIF levels. Their conclusion: “These results…imply that the mechanism by which submucosal myomas impact endometrial receptivity is not simply a local mechanical effect over the myoma, but involves a signaling mechanism to the entire endometrium.” These results help to explain the reproductive dysfunction clinically observed in women with submucosal myomas, and supports the recommendation for removal of submucosal myomas in women with infertility or recurrent pregnancy loss.

In recent years, we have witnessed an appreciation of the multisystem benefits of vitamin D, along with a realization that vitamin D insufficiency approaches endemic proportions.

Our experts at Yale Reproductive Endocrinology are engaged in furthering an understanding of the relevance of vitamin D in women’s health. Dr. Pal and colleagues had previously shown significantly higher clinical pregnancy rates in association with higher levels of vitamin D metabolite in the ovarian follicular fluid of women undergoing IVF; in this same study, serum and follicular fluid levels of 25OH vitamin D, a metabolite of vitamin D that reflects the status of overall body stores, were highly correlated and identified follicular fluid levels as reliably reflecting serum levels of the metabolite. Dr. Taylor’s laboratory has identified that endometrial implantation markers were modulated by exposure to vitamin D, identifying at least one mechanism whereby vitamin D status may impact reproductive success. In light of these observations, our team encourages assessment of vitamin D status as an integral part of infertility management, and aggressive repletion of stores is advised for all considering pursuit of infertility treatment.

Given the fact that insulin resistance and inflammation are not only recognized concomitants of vitamin D insufficiency but are also pivotal in the pathophysiology of polycystic ovary syndrome (PCOS), a pilot trial of vitamin D and calcium supplementation in PCOS was recently completed (principal investigator: Lubna Pal). Results of this trial were presented at the annual meeting of the American Society for Reproductive Medicine in October 2010 and generated much enthusiasm, as the therapeutic efficacy of vitamin D and calcium in PCOS is suggested by the preliminary data, although these observations merit substantiation in larger studies.

Vitamin D deficiency has been linked to maternal risk for developing pre-eclampsia and gestational diabetes. The importance of maternal vitamin D stores for fetal well-being is also being appreciated, and maternal serum 25OHD levels have been shown to relate to the progeny’s skeletal integrity well beyond the neonatal period. In collaboration with international colleagues, Dr. Pal is studying the burden of vitamin D insufficiency in gravid women in the developing world.

The overarching aim of these endeavors is to explore the possibility that aggressive vitamin D repletion, an economical, easily accessible and safe strategy, may hold promise of enhancing reproductive potential and mitigating maternal and child morbidity.
Original Research Articles: 2009


Pal L, Santoro N. Resolving the dilemma about menopausal hormone therapy: Playing for KEEPS. Commentary on KEEPS trial. Contemporary Ob/Gyn, August 2009.


Original Research Articles: 2010


Seli E, Arici A. Ovulation Induction with clomiphene citrate. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA, 2010.


Taylor HS. Approaching the ideal selective estrogen receptor modulator (SERM) for the prevention and treatment of postmenopausal osteoporosis. Formulary (Cover Article) 2010 45:52-61.

Taylor HS, Mansur J. Hormone therapy use in Menopause. JCEM (In Press).

The Section of Gynecologic Oncology provides specialized care for women with gynecologic malignancies. Our mission is to mentor residents and fellows in our program, conduct basic and translational research, increase patient and referring physician awareness of early warning signs of gynecologic malignancy, and expand the treatment horizons for women with gynecologic cancers. We employ a multidisciplinary approach to comprehensive management of gynecologic malignancies and offer clinical trial participation as a member of the Gynecologic Oncology Group for national cooperative study group trials of cancer therapies as well as multiple pharmaceutical company and physician-sponsored trials. We have a very active early detection, novel treatment and prevention program for ovarian cancer. Each physician emphasizes a minimally invasive approach to gynecologic cancer surgery.

OUR PHILOSOPHY AND MISSION

Thomas J. Rutherford, PhD, MD, Section Chief, Associate Professor
Interests: Ovarian, uterine, vaginal, cervical and vulvar cancer; difficult gynecologic surgery; unknown primary cancer; brachytherapy; gestational trophoblastic neoplasia, quality of life in cancer survivors

Peter E. Schwartz, MD, Vice Chair for Gynecology, Professor
Interests: Ovarian, uterine, vaginal, cervical and vulvar cancer; difficult gynecologic surgery; screening for ovarian cancer; gestational neoplasia; brachytherapy

Alessandro D. Santin, MD, Professor
Interests: Cancer of the ovary, uterus, vagina, cervix and vulva; intraperitoneal chemotherapy, tumor immunology and immunotherapy; tumor angiogenesis; radiation biology; experimental therapeutics in gynecologic oncology

Masoud Azodi, MD, Associate Professor
Interests: Minimally invasive surgery, robotic surgery, pre-malignant and malignant gynecologic disorders involving the vulva, cervix, vagina, uterus, ovaries and placenta

Dan Silasi, MD, Assistant Professor
Interests: Ovarian, uterine, vaginal, cervical and vulvar cancers

Ernest I. Kohorn, MD, Professor Emeritus
Interests: Gestational trophoblastic disease

New Faculty:
Elena Ratner, MD, Assistant Professor
Interests: Ovarian, uterine, vaginal, cervical and vulvar cancers; quality of life in cancer survivors

Affiliated Ob/Gyn Basic Science Faculty:
Gil Mor, MD, PhD
Yingqun Huang, PhD

For full bios of our Gynecologic Oncology physicians, please visit http://medicine.yale.edu/obgyn/gynonc/people/index.aspx
including laparoscopic staging, radical vaginal surgeries and radical trachelectomy. Each physician is certified to perform surgeries robotically.

**Education and Training**

An important mission of our Section is to teach residents to evaluate and counsel women and their families regarding malignancies, including treatment options, complications and success of treatment. Residents participate in the operating room and manage pre- and postoperative care. Our fellowship program teaches the diverse treatment options for, and complications of, gynecologic cancers. This training requires one research year that leads to a study designed by the fellow.

**Clinical/Research Services**

We endeavor to provide the best possible care for our patients and their families in an environment of respect, compassion and sympathetic concern. Patients are informed about all treatment options, including their advantages and disadvantages.

The Section focuses on clinical care and translational research in the areas of endometrial, cervical and ovarian cancer. We are searching for specific early markers of ovarian and endometrial cancer, we continue investigating the molecular pathways responsible for chemoresistance in ovarian cancer, and we continue to develop new markers to predict chemoresponsiveness.
We have continued to develop the Yale Ovarian Cancer Early Detection Program, and it now utilizes ultrasonography, serum blood markers, physical examination and genetic counseling to determine a composite risk score.

**ACCOMPLISHMENTS 2009-2010**

1. Clinical volume continues to increase. We currently have outreach programs in nine affiliated hospitals.

2. We have active protocols for cervical, vulvar, vaginal, endometrial, ovarian, fallopian tube and peritoneal cancers. Our Section has applied the use of robotic surgery in over 500 cases. We are continuing to develop our bone density screening program for women treated with pelvic radiation or chemotherapy and for those patients who are placed in surgically induced menopause.

3. Our Section recruited a sixth gynecologic oncologist this year, Dr. Elena Ratner. Dr. Ratner completed her residency and gynecologic oncology fellowship at Yale and is also supported by an NIH Women’s Reproductive Health Research (WRHR) grant (K12 award). She is conducting basic research into the genetic susceptibilities for ovarian cancer.

**GOALS 2010-2011**

1. Expand the number of NIH grants held by the Section and affiliated Yale Ob/Gyn “Discovery to Cure” scientists.

2. Develop new research thrusts that are compatible with our current programs, as well as support expansion of our outreach services.
Endometrial cancer is the most common female genital tract malignancy in the United States, with an incidence of 40,100 new cases and 7,470 deaths in the United States in 2009. Type I endometrial cancers, which account for the majority of cases, are usually well differentiated and endometrioid in histology. These neoplasms are frequently diagnosed in younger women, are typically associated with a history of hyperestrogenism, and generally have a favorable prognosis with appropriate therapy and a five-year survival rate of 90%. In contrast, Type II endometrial cancers include poorly differentiated endometrioid tumors (G3-EEC), serous papillary (USPC) and clear cell endometrial cancers. Type II disease has a substantially poorer prognosis. While only 15% to 20% of endometrial cancer patients have Type II disease, most of the recurrences and deaths take place in this population.

A novel antibody-like molecule called ICON—short for Immuno-Conjugate—may hold promise for women with these highly aggressive gynecologic malignancies. ICON was developed by Yale researchers and is composed of two human factor VII molecules fused to a human immunoglobulin G1 Fc molecule. It binds Tissue Factor (TF), which is inappropriately expressed by tumor cells and endothelial cells in the vasculature of aggressive Type II endometrial cancer. Researchers have found that tumor cells characterized by high concentrations of TF and vascular endothelial growth factor (VEGF) generate solid tumors with an intense vascularity and high aggressive behavior. Several studies have shown that tumor cell TF plays an important role in metastasis, possibly by inducing the coating of the tumor cell with fibrin that traps the cells in the microvasculature, aiding the metastatic process.

To test the effectiveness of targeting tumor TF with ICON in USPC—one form of Type II endometrial cancer—Dr. Alessandro Santin and his associates at Yale applied the drug to these cells in vitro to determine its cytotoxicity. They first determined that cytoplasmic and/or cell membrane TF existed in all the cancer cells tested (16 of 16); but they found little TF expression in cells taken from normal endometria not exposed to progestins. They also found high expression of TF in three of the six USPC cell lines. Most importantly, the researchers discovered that ICON was quite effective in destroying USPC cells.

While clinical trials are needed to verify ICON’s cancer cytotoxicity in vivo in humans, the Yale team is hopeful that the new agent may represent a novel therapeutic agent for the treatment of patients harboring advanced, recurring and/or metastatic USPC refractory to standard protocols.
SeleCteD keY puBliCAtions 2009-2010


Letters

Santin AD. Letter to the Editor referring to the manuscript entitled: “Phase II trial of trastuzumab in women with advanced or recurrent HER-positive endometrial carcinoma: a Gynecologic Oncology Group study” recently reported by Fleming et al. (Gynecol Oncol., 116:15-20;2010). Gynecol Oncol. 2010 Jul;118(1):95-6; author reply 96-7. Epub 2010 Feb 20.
Richard Bercik, MD, Assistant Professor, Section Chief, Urogynecology and Reconstructive Pelvic Surgery
Interests: Minimally invasive surgery for prolapse and incontinence including advanced laparoscopic surgery, use of new material for prolapse repair, diagnostic and treatment modalities for urinary and fecal incontinence, pelvic organ prolapse, pelvic floor disorders, office cystoscopy, biofeedback for urinary and fecal incontinence, pelvic floor reconstruction, vaginal hysterectomy for the enlarged uterus, vaginal fistulae

Kathleen Connell, MD, Assistant Professor, Director of Research, Urogynecology and Reconstructive Pelvic Surgery
Interests: Genetic causes of pelvic floor disorders, diagnostic and treatment modalities for urinary and fecal incontinence, pelvic organ prolapse, pelvic floor disorders, interstitial cystitis, office cystoscopy, pelvic floor muscle rehabilitation and biofeedback for urinary and fecal incontinence, advanced laparoscopic surgery, pelvic floor reconstruction, incontinence procedures, vaginal fistulae

Marsha K. Guess, MD, MS, Assistant Professor, Fellowship Director
Interests: Cellular causes of pelvic floor disorders, vaginal and abdominal pelvic reconstructive surgery, advanced laparoscopic pelvic floor muscle rehabilitation and biofeedback for urinary and fecal incontinence surgery, transurethral collagen injections for pelvic floor disorders, pelvic organ prolapse, sexual dysfunction

Elisabeth A. Erekson, MD, MPH, Assistant Professor
Interests: Quality measures for surgical outcomes, vulvar symptoms in urinary incontinence, obstructive bowel symptoms, diagnostic and treatment modalities for urinary and fecal incontinence, pelvic organ prolapse, pelvic floor disorders, interstitial cystitis

Cherrilyn Richmond, MS, APRN, WHNP, Women’s Health Nurse Practitioner
Interests: Pelvic muscle floor rehabilitation or training, electrical stimulation, behavioral modification, frequent urinary tract infection, urinary frequency and urgency, pessary fitting, urodynamics studies, cystoscopy, rectocele, cystocele, sexual dysfunction

For full bios of our Urogynecology and Reconstructive Pelvic Surgery physicians, please visit
http://www.yaleobgyn.org/people/urogyn.aspx

We endeavor to provide the best possible care for our patients in an environment of respect, compassion and concern. Best care means not only choosing treatments with established excellent outcomes, but also tailoring treatments that best fit the patient’s lifestyle, goals and expectations. We are committed to ensuring that the patient is accurately and fully informed about all of her treatment options. Furthermore, our Section integrates resident and fellowship training, medical student education, community outreach and research to enhance and improve the care of those patients with pelvic floor disorders.
Education and Training

Resident physicians and fellowship trainees are actively involved in the clinical and research activities of the Section. The fellowship in Female Pelvic Medicine and Surgery is a three-year ABOG-accredited training program with one fellow per year. Currently a third- and fourth-year resident also participate in the clinical practice as they learn to evaluate women with pelvic floor disorders. Several residents are also actively involved in clinical and basic research projects. On average, one graduating resident per year chooses to pursue a career in urogynecology. Gynecologic surgeons from throughout the United States and abroad regularly visit to observe recently developed surgical techniques. Faculty members have traveled abroad to demonstrate new techniques and to lecture to gynecologic surgeons in Europe and Australia.

Clinical Services

Our faculty members have advanced training in managing disorders of the female pelvic floor and continue to expand their clinical tools. Three faculty members are now actively performing robot-assisted laparoscopic hysterectomy and pelvic floor repair surgeries. Our facility has become a referral center for the management of mesh-related complications including pain, erosion and contraction. The Section continues to provide management options for women with pelvic floor disorders (PFD), including:

- Comprehensive evaluations of PFD, which may include urodynamic testing, office cystoscopy and pelvic floor muscle evaluation
Pelvic floor rehabilitation with biofeedback and electrical stimulation
Office testing for spinal neuromodulation
Office-based neuromodulation for overactive bladder
Myofascial release technique for dyspareunia
Urethral collagen injections
Minimally invasive surgical options including laparoscopic and vaginal techniques
Advanced surgical techniques for re-operative repairs for the failure of prior reconstructive pelvic surgeries

Research

Research continues with investigation of the molecular and cellular mechanisms of pelvic organ prolapse and the role of vaginal smooth muscle function and genetic factors in pelvic organ prolapse. New clinical trials have begun to enroll patients, including studies investigating the association of vulvar symptoms with urinary incontinence and the use of vibratory sensation to predict the success of neuromodulation for overactive bladder patients. Established trials looking into non-medical treatments for female sexual dysfunction continue to enroll subjects.

ACCOMPLISHMENTS 2009-2010

• Poster presentations at American Urogynecologic Society (AUGS) and SGI Annual Meetings 2009.
• Secured ABOG certification for the Female Pelvic Medicine and Surgery Fellowship.
• Increased new patient visits; had a 15% increase in major surgical repairs with more than 400 major repairs annually.
• Awarded Pepper Center grant to investigate prolapse treatment in the geriatric population and an AUGS grant to investigate neuromodulation.
- New treatment modalities added, including robot-assisted laparoscopic hysterectomy and pelvic floor repair surgery.

- Started an educational and practice location at our affiliate, Bridgeport Hospital.

- Cherrilyn Richmond, our nurse practitioner, and Dr. Elisabeth Erekson participated in the Yale Haiti relief project and traveled to the Dominican Republic to provide much-needed health services to victims of the Haiti earthquake.

- Continue research into genetic and molecular causes of pelvic floor disorders with presentation and publication of these important results.

- Complete enrollment in two clinical trials for overactive bladder.

- Increase NIH funding.

- Establish a new practice site in Old Lyme.

**GOALS 2010-2011**

![Urogynecology Patient Volume Growth](image)

*Figure 1*
Sacrocolpopexy is a procedure for correction of pelvic organ prolapse that involves the placement of graft material in the anterior and posterior vagina and the attachment of this material to the sacrum. This procedure has long been considered the gold standard for treating vaginal apical prolapse. However, since sacrocolpopexy has traditionally been performed via an abdominal approach, concerns about the morbidity of an abdominal operation and the recovery associated with an abdominal incision have limited its use.

Robot-assisted laparoscopic surgery provides the surgeon the ability to perform complex dissection and suturing without the morbidity of an abdominal incision. Robot-assisted laparoscopic sacrocolpopexy is rapidly being incorporated into the practice of urogynecology across the country. The robot-assisted procedure uses five small trocar incisions of less than a centimeter each. Advantages of this approach over the standard abdominal procedure include significantly less pain, fewer adhesions, less bleeding, a shorter hospital stay, and a quicker recovery and return to normal activities.

In October 2009, Dr. Elisabeth Erekson of the Yale Section of Urogynecology performed the first robot-assisted laparoscopic sacrocolpopexy at Yale New Haven Hospital. Since that time Drs. Richard Bercik and Kathleen Connell have also begun to offer the procedure. Women considering surgery for the correction of pelvic organ prolapse now have this minimally invasive approach as an option for their repair.

Yale is one of only two centers in Connecticut offering robot-assisted laparoscopic sacrocolpopexies. According to Dr. Erekson, “The robot gives you superior visual cues to facilitate dissection and ease the surgery. The robot holds the camera steady for excellent visualization. It’s an exceptional assistant that never gets tired. This is important and exciting for our section to be able to offer to women considering surgery.”

ROBOTS ARE NO LONGER JUST SCIENCE FICTION – NOW THEY ARE PART OF CLINICAL PRACTICE
SELECTED KEY PUBLICATIONS 2009-2010


Erekson EA, Kassis N, Washington BB, Myers DL. The association between Stage II or greater posterior vaginal prolapse and obstructive bowel symptoms. *Female Pelvic Medicine and Reconstructive Surgery* 2010; 16(1): 59-64.


**Scientific Presentations**


The Section of Family Planning provides specialized care for women with reproductive planning needs. In addition, our Section strongly emphasizes resident education in all aspects of family planning services.

We endeavor to provide the best possible care for our patients in an environment of respect, compassion and sympathetic concern. Best care also means that the patient is accurately informed about all of her treatment options, including advantages and disadvantages.

An important mission of our Section is to educate residents about our subspecialty. Second-year residents have a six-week Family Planning rotation, during which they learn to evaluate and counsel women regarding the complete spectrum of contraceptive and sterilization options, and to provide appropriate non-surgical and surgical treatments.
for undesired or abnormal pregnancy, should they so choose. Residents participate in the Section’s surgical cases, pre- and postoperative care, ambulatory procedures in the Yale-New Haven Hospital Women’s Center, and didactic sessions. Residents serve as first assistant in all of the Section’s surgical cases. Training in gynecologic ultrasound is of paramount importance in obstetrics and gynecology, and residents rotating through the Section of Family Planning have ample hands-on experience in this modality. We believe that the knowledge and surgical skills gained from these activities will allow our residents to evaluate and manage a wide range of family planning related office gynecologic issues.

Another mission of our Section is to increase our understanding of women’s reproductive health issues and to formulate new or improve existing treatments. At present, the focus of the Section’s research includes the development of new contraceptive methods and the study of the mechanisms of action of currently available modalities such as the IUD and long-term progestin-only approaches. Residents are encouraged to participate in the Section’s ongoing research projects.

One of the weekly Planned Parenthood sessions includes training and experience in contraceptive counseling, provision of all currently available methods, and observation of professional counseling sessions with the
Residents receive hands-on training in the selection, use and monitoring of all available options, including combination oral, transdermal and vaginal hormonal preparations; ParaGard and Mirena IUDs; Implanon, Depo Provera and oral forms of long-term progestin-only contraception; and the condom, diaphragm and cervical cap.

The program is affiliated with the Ryan Residency Training Program. The Ryan Program is an education initiative that assists Ob/Gyn residency programs to fulfill their mandate to train future Ob/Gyn physicians in abortion methods. It is named after Kenneth J. Ryan, a reproductive scientist, ethicist and long-time Chair at Harvard Medical School, who founded the first teaching hospital-based abortion and family planning clinic.

ACCOMPLISHMENTS 2009-2010

The Section of Family Planning continued its academic and programmatic growth during FY 09-10 as demonstrated by the following:

1. Re-approval for funding via the Ryan Residency Training Program.
2. Continuation of collaborative clinical rotation for PGY2 residents at the New Haven Planned Parenthood site.
3. Improved and expanded lecture series in family planning-abortion services.

GOALS 2010-2011

1. Recruit additional faculty to Section.
2. Continue growth of clinical practice.
3. Open additional clinical research protocols with eventual entry into the NICHD Contraceptive Clinical Trials Network.

RESEARCH LABS
GAMETE BIOLOGY GROUP

Six internationally recognized researchers lead the Gamete Biology Research Group, spearheading laboratory projects that include both translational research with direct clinical implications and basic molecular investigations into gene expression in embryos and gametes. Their research covers a broad range of categories, including female and male reproduction, preimplantation embryo development and gonadal development.

The laboratory’s research in female reproduction investigates: 1) DNA repair in the mammalian oocyte; 2) the role of FSH receptor variants in infertility; 3) translational control of gene expression in the mammalian oocyte and early embryos; 4) mRNA gene expression profiles in cumulus cells and in human oocytes at different maturational stages; 5) factors that control the quality and number of eggs found in ovaries; and 6) how stress and nutrition control the growth and death rates of ovarian follicles that contain egg cells.

Research on male reproduction covers: 1) sperm quality in the aging man; 2) paternal effects on reproductive outcome; 3) mammalian sperm DNA and the infertile male; and 4) apoptosis during spermatogenesis and in mature spermatozoa.

Investigators concentrating on preimplantation embryo development are looking at: 1) non-invasive assessment of embryo viability in assisted reproduction; 2) characterizing the gene expression profiles of human embryos and gametes; and 3) assessing the developmental capacity
and growth patterns of normal and abnormal embryos.

Finally, Yale researchers studying gonadal development have been investigating: 1) gonad development in the fetus and 2) developmental establishment of stem cell “niches,” or compartments, that support the developing and adult ovary.

Gabor Huszar, MD, Senior Research Scientist, Director, Sperm Physiology Laboratory
gabor.huszar@yale.edu

Joshua Johnson, PhD, Assistant Professor
josh.johnson@yale.edu

Maria Lalioti, PhD, Assistant Professor
maria.lalioti@yale.edu

Pasquale Patrizio, MD, MBE, Professor, Director, Yale Fertility Center
pasquale.patrizio@yale.edu

Denny Sakkas, PhD, Associate Professor, Director of Assisted Reproduction Laboratories
denny.sakkas@yale.edu

Emre Seli, MD, Associate Professor, Associate Director for Research, Section of Reproductive Endocrinology and Infertility
emre.seli@yale.edu
One of goals of the Gamete Biology laboratories has been to find objective biochemical markers of sperm maturity and function to help assess male fertility. Dr. Gabor Huszar’s lab has developed a sperm-hyaluronic acid binding assay and an IVF-ICSI sperm selection method that are now being utilized around the world. Their research has found that sperm that are able to bind to hyaluronic acid have completed the plasma membrane remodeling step during development, have no attributes of diminished maturation, and have sperm morphology characteristic of sperm that can successfully bind to the zona pellucida of oocytes prior to fertilization. This assay can help clinicians determine the proportion of sperm in a patient’s ejaculate that has a greater likelihood of producing a viable pregnancy.

The lab has also found that hyaluronic acid-bound sperm are devoid of DNA degradation, a major cause of infertility. These sperm show a very low normal frequency of chromosomal aneuploidies, no matter how high the frequencies are in the respective semen in which the selected sperm originated.

The new sperm-hyaluronic acid binding assay also has implications for couples who are treated with intracytoplasmic sperm injection (IVF-ICSI).

In a recent large randomized clinical study, approximately 800 ICSI couples were enrolled: 400 couples were injected with sperm selected by sperm shape judged by the embryologist, and the other 400 were treated with sperm selected by hyaluronic acid binding. The study indicated that couples treated with hyaluronic acid binding selected sperm may see a 25%-30% increase in pregnancy rates, compared to the group in which the sperm was selected by shape attributes.

Worrilow et al: Multi-site clinical trial evaluating PICSI, a device for hyaluronan-mediated sperm selection for ICSI. ESHRE 2009 annual meeting, Rome, Italy.
Infertility centers attain relatively high success rates following in vitro fertilization (IVF), in many cases through the simultaneous transfer of multiple embryos. Consequently, more than 30% of IVF pregnancies are twins or higher-order multiple gestations, and 51% of all IVF neonates are the products of multiple gestations. Today, decreasing multiple gestations while maintaining or improving overall pregnancy rates remains the most pressing contemporary goal in the treatment of infertility.

A key issue surrounding multiple gestations following IVF is the inability to precisely estimate the viability of individual embryos. Grading systems based on embryo morphology and cell division rates have been the mainstay of embryo assessment worldwide. Unfortunately, they are not sufficiently precise to compel most patients and clinicians to reduce the number of embryos transferred to a point where twins are uncommon and higher-order multiple gestations are rare or eliminated entirely.

Drs. Emre Seli and Denny Sakkas have recently reported results from a multi-center study using a non-invasive spectroscopic method for prediction of the implantation potential of embryos in IVF. In this study, they showed that the metabolism of embryos that result in pregnancy is different than that of embryos that do not, and that the difference may be detected by the rapid, non-invasive evaluation of the embryo culture media using spectroscopic analysis and bioinformatics, also called metabolomics. The team evaluated spent IVF culture media of transferred embryos using near-infrared (NIR) spectroscopy. Their approach successfully yielded a pattern that predicted the implantation potential of embryos and was independent of morphology as a parameter. Most importantly, their findings suggest that the addition of this technology to morphologic assessment may improve our ability to determine the viability of individual embryos. The use of such a rapid, non-invasive, objective and affordable technology has the potential to decrease multiple gestations and improve pregnancy rates in the near future.


**EMBRYO METABOLISM MAY HELP DETECT VIVABLE EMBRYOS**
**SELECTED KEY PUBLICATIONS 2009-2010**


The Maternal-Fetal Sciences Group seeks to develop therapeutic interventions for major complications of pregnancy through an integration of clinical, translational and basic science research approaches. Studies focus on preterm delivery (PTD), preeclampsia (PE), intrauterine growth restriction (IUGR) and recurrent pregnancy loss, all leading causes of maternal, fetal and neonatal morbidity and mortality.

Research in Dr. Charles Lockwood’s lab on PTD specifically seeks to dissect the mechanism through which abruption and infections lead to functional progesterone withdrawal by down-regulating reproductive tract progesterone receptor expression. Research efforts by Dr. Irina Buhimschi’s lab seek to leverage proteomic and gene array methodologies to identify novel markers of PTD and PE, which will facilitate the development of new diagnostic and therapeutic strategies. Studies by Dr. Seth Guller aimed at understanding the role of extracellular matrix remodeling in the placenta and myometrium will enable implementation of procedures that limit fibrosis at the uterine-placental interface associated with IUGR.

Another focus of the Lockwood lab is the analysis of the interaction of uterine, placental and immune cells in the etiology and pathophysiology of PTD, PE and IUGR. Studies using gene array analysis have established patterns of decidual chemokine response to inflammatory stimuli, prompting investigation of the role of dendritic cells—specialized antigen presenting immune cells—in the etiology and pathophysiology of PE. Related studies include the evaluation of separate and interactive effects of ovarian steroids and pro-inflammatory cytokines on the expression of members of the NK cell and macrophage recruiting family of cytokines. The role of Toll-like receptors, mediators of the innate immune response, in first trimester trophoblast-macrophage interactions is also being explored using co-culture and state-of-the-art molecular methodologies.

In addition to studying placental Toll-like receptors, Dr. Vikki Abrahams’ lab is working to understand the role of Nod-like receptors and the inflammasome in trophoblast responses to infections, and how such innate immune functions can impact pregnancy outcome. Another area of ongoing research in the Abrahams lab is the mechanism of pregnancy complications in autoimmune diseases like...
lupus and antiphospholipid syndrome. Through these studies, their team is hoping to develop more effective strategies for diagnosis, treatment and prevention of autoimmune-associated obstetrical complications.

The differential roles of placental and renal synthesis of the angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) and their antagonist soluble fms-like tyrosine kinase-1 (sFlt-1) in pregnancy-induced hypertension and proteinuria are under study by Dr. Catalin Buhimschi using animal models and placental and kidney cell cultures. The specific role of hypoxia and plasminogen activator inhibitors, major regulators of fibrinolysis and cell invasion, in the pathophysiology of IUGR and PE is under investigation using primary cultures of human placenta and a dual perfusion model.

A major interest of Dr. Mor’s laboratory is the field of reproductive immunology. As the principal investigator of a large NIH-supported Program Grant (P01), Dr. Mor has performed experiments that show that viral infection of the placenta can elicit a fetal inflammatory response. That, in turn, can cause organ damage and potentially downstream developmental deficiencies. Furthermore, they demonstrate that viral infection of the placenta may sensitize the pregnant mother to bacterial products and promote preterm labor. These studies suggest that it is important to take into consideration the fact that during pregnancy it’s not only the maternal immune system that responds, but also the fetal/placental unit. These results further support the immunological role of the placenta and the fetus in affecting the global response of the mother to microbial infections. This is relevant for making decisions associated with treatment and prevention during pandemics.
Preterm birth is currently the largest public health problem facing Ob/Gyns, which is why the Yale Department of Obstetrics, Gynecology and Reproductive Sciences has made it one of its top research priorities. One of the goals of Dr. Catalin Buhimschi’s research is to identify biomarkers that characterize preterm birth, and his team has devoted a great deal of time to studying the proteomic markers associated with intrauterine inflammation and infection.

The researchers have attempted to identify biomarkers that are characteristic of fetal infection and are trying to determine how these biomarkers can predict the occurrence of complications associated with prematurity, including cerebral palsy, neurological damage and intraventricular hemorrhage. In a recently published paper in the *American Journal of Pathology*, Dr. Buhimschi and associates reported on biomarkers involved in inducing fetal brain damage in animal studies. These markers have also been identified in humans, and belong to a class of molecules called antimicrobial peptides, which include defensin-2, defensin-1, S100A12 and S100A8.

Of course, one of the questions clinicians and patients ask when they hear of such basic research is: How far are we from clinical application in general practice? Dr. Buhimschi has conducted a variety of human studies to test the accuracy of these biomarkers as a diagnostic tool. The team is testing a proteomic platform that involves new technology incorporating antibodies on a special bead. Their goal is to quickly quantify one of the cytokines—interleukin 6—and to figure out how they can make the test rapidly available to clinicians in the trenches. There is already a company investing in the technology, and the hope is that the test will be available commercially in the near future.

Preeclampsia has also been a major focus of research at Yale in recent years. Our goal is to determine the role of angiogenic factors in the disease. Dr. Buhimschi and associates have discovered that the ratio of two angiogenic factors accurately predicts the occurrence of preeclampsia and can be used to diagnose the disorder. Their research suggests that a ratio of about 2:1 between Soluble fms-like tyrosine kinase-1 (sFlt-1) and Placenta Growth Factor-1 (PLGF) in the urine of pregnant patients is predictive of moderate to severe preeclampsia.
To better understand the ways in which cancer cells disrupt the normal mechanisms that control cell growth, the Yale Gynecologic Cancer Biology Group studies various aspects of cell signaling that cause or support carcinogenesis. Not content to concentrate our efforts on basic research, we have focused our attention on translating the lab’s findings into clinical practice. These well-funded laboratories are using the knowledge gained from basic studies of inter- and intracellular communication through both membrane and nuclear receptors to devise novel methods for cancer diagnosis and therapy.

Steroid hormone receptors are ligand activation transcription factors, members of the nuclear receptor family that controls many important physiological functions. Their control of the transcription of specific genes is one important mechanism that is frequently disrupted in cancers of the reproductive tract. For example, estrogens are known to play an important role in breast and endometrial cancer; androgens in prostate cancer. Dr. Richard Hochberg’s laboratory is designing and synthesizing biologically active derivatives of steroid hormones for diagnostic and therapeutic purposes and for investigation of hormone action. His laboratory has synthesized estrogens, labeled with $^{123}$I for SPECT imaging of breast cancer, and androgens labeled with $^{18}$F for PET imaging of ovarian and prostate cancers. These radio-labeled compounds allow the detection and localization of cancers by hormone receptor mediated uptake. His laboratory has also synthesized locally active estrogens for
the treatment of dyspareunia in women for whom estrogen therapy is contraindicated (e.g., by breast cancer) as well as SERMs for the treatment of menopausal symptomology.

In addition to these nuclear receptors, cell surface receptors such as EGFR and HER2 play a key role in regulating tumor cell growth. Dr. Nita Maihle’s laboratory has contributed to our understanding of these membrane-associated oncogenic signaling pathways that play a vital role in controlling breast, endometrial and ovarian cancer cell growth. They have used this information to predict mechanisms of drug resistance in response to biologically targeted chemotherapeutics such as trastuzumab (Herceptin). In addition, her laboratory has discovered and pioneered the clinical application of a novel class of circulating biomarkers, soluble EGF receptors, designated sEGFR, that have been shown to have diagnostic, prognostic and “theranostic” (i.e., both therapeutic and diagnostic value) utility in breast cancer patients as well as in certain gynecologic malignancies.

Dr. Yingqun Huang has been studying the RNA-binding protein Lin28 in ovarian cancer cells, and has shown that specific repression of Lin28 using siRNA results in decreased cell proliferation and that increased expression of Lin28 accelerates cell proliferation. The former cells exhibit multiple characteristics of embryonic stem cells and are consistent with being ovarian cancer stem cells. In keeping with their role in cell cycle regulation, Dr. Huang is focusing on the further dissection of the molecular mechanisms and pathways involved in Lin28-mediated regulation of cell growth. She is also investigating the use of the folate receptor, which is over-expressed in epithelial ovarian cancer cells, to deliver therapeutic siRNAs specifically to cancer cells. She is
developing a new strategy to couple the vitamin folate to siRNAs and to test whether these siRNAs can be delivered to folate receptor-expressing cells to elicit specific and efficient gene silencing and thereby cancer cell death.

Dr. Gil Mor’s laboratory has also identified, isolated and characterized ovarian cancer stem cells. These cells represent the source of tumor recurrence as well as chemoresistance. The Mor laboratory has identified a unique microRNA profile that differentiates ovarian cancer stem cells from other malignant ovarian cells. One of these, mir-199A, is a major regulator of the NFkB pathway, and could be used as a therapeutic target and a marker for differentiation. Recent studies in Dr. Mor’s laboratory have shown that ovarian cancer stem cells are a source of VEGF-independent neovascularization, which might explain the late failure VEGF inhibitors. In the therapeutic area, the laboratory has identified a new compound that targets ovarian cancer stem cells by inhibiting the mTOR pathway. The molecule represents a potentially important therapeutic agent for the treatment of ovarian cancer. An additional compound identified by the laboratory functions as an NFkB inhibitor, preventing ovarian cancer stem cells’ self renewal. These therapies are meant to be applied for the prevention of recurrence, the major problem in the treatment of ovarian cancer patients.

Molecular studies done in Dr. Mor’s laboratory include investigation of the role of TWIST, a transcriptional factor associated with embryonic differentiation, in the process of tumor growth and tumor repair. Ongoing studies are focusing on the use of TWIST as a marker for identifying metastasis as well as a target for prevention of metastasis.

Dr. Alessandro Santin’s laboratory has recently completed a trial involving vaccination of cervical cancer patients harboring the human papillomavirus (HPV) 16 and 18 genotypes with an FDA-approved therapeutic vaccine developed in his laboratory based on autologous monocyte-
dendritic cells (DC) loaded with full-length HPV16 or 18 E7 oncoproteins. All vaccinated patients responded to the therapeutic vaccination in the absence of any significant side effects. The Santin lab has also reported the novel use of trastuzumab, an anti-HER2neu humanized antibody FDA-approved in breast cancer patients and in patients with chemotherapy-resistant uterine serous papillary carcinoma (i.e., the most biologically aggressive subtype of endometrial carcinoma). Dr. Santin’s laboratory is currently studying the potential therapeutic efficacy of pertuzumab, the newly developed anti-HER2neu humanized antibody (Genentech Corp.), against ovarian clear cell carcinomas and uterine serous tumors harboring the amplification of the c-erbB gene. Anastrozole (Arimidex), an aromatase inhibitor approved by the FDA for breast cancer patients, is also under investigation by Dr. Santin’s research group in patients harboring chemotherapy-resistant endometrial carcinoma, with encouraging clinical results.

Richard Hochberg, PhD, Professor
richard.hochberg@yale.edu

Yingqun Huang, MD, PhD, Associate Professor
yingqun.huang@yale.edu

Nita Maihle, PhD, Professor
nita.maihle@yale.edu

Gil Mor, MD, PhD, Professor
gil.mor@yale.edu

Alessandro Santin, MD, Professor
alessandro.santin@yale.edu
Drs. Gil Mor and Yingqun Huang, two Yale investigators, have found evidence to suggest that targeting cancer stem cells within an ovarian tumor may help to conquer this insidious disease.

Until recently, the challenge for clinicians has resulted from the fact that almost 90% of women with ovarian cancer relapse within five years, even after optimal debulking. Why is that? The work done in the Yale Department of Ob/Gyn suggests that ovarian cancer cells are not as homogeneous as we once thought. When these cells are cultured, we find that most divide very quickly, but a small subset grows quite slowly. In the past, researchers have assumed that the fast-dividing cells were the ones to concentrate on when looking for effective chemotherapeutic agents. But these Yale investigators decided to pay more attention to the slow-growing cells, and as a result they discovered that they have all the molecular characteristics of adult stem cells.

A brief review of stem cell physiology will shed some light on why this discovery is so important: If you cut your skin, it’s not epithelial cells that heal the wound but rather adult stem cells in the area of the wound that are able to produce epithelial cells to replace the damaged cells. In simple terms, one reason humans look the same over the years is because these stem cells have a memory of what we look like.

Similarly, the Yale team has isolated stem cells that have a memory of cancer cells. Dr. Huang, for instance, has found that some ovarian cancer cells express Lin28 and Oct24, two major proteins found in embryonic stem cells. Because neither protein is typically found in differentiated cells, Huang believes that cells expressing these compounds may in fact represent ovarian cancer stem cells. Dr. Mor’s lab isolated the cells using a different strategy, which exploited their inflammatory phenotype.

Cancer stem cells (CSCs) have been described in other cancers, including hematopoietic, brain and breast cancers, but evidence for their existence in ovarian cancers is just beginning to emerge. Because CSCs give rise to other populations of cancer cells found in the original tumor, they are thought to be responsible for tumor initiation, growth, metastasis and relapse, and may represent crucial targets for therapies. Mor and Huang theorize that the reason ovarian cancer recurs so frequently is that standard platinum and Taxol-based chemotherapy eliminates the fast-dividing, more differentiated daughter cells but does not affect the stem cell that they are derived from. Killing the stem cells selectively might not only treat the cancer but also prevent the relapses that often occur after currently available chemotherapies.
Working on the theory that these putative stem cells represent the source of reoccurrence and metastasis, the Huang lab was recently able to show that stopping the genetic expression of Lin28 and Oct4 does in fact reduce ovarian cancer cell growth and survival. So determining whether such stem cells are present after surgery is critical in order to determine the best type of treatment!

Dr. Gil Mor’s research team has just finished a study in which they found that if a patient has a high percentage of ovarian cancer stem cells, the cancer is much more likely to recur, even if she has localized stage 1 and 2 disease. They are currently screening for therapeutic agents that would target these cancer stem cells, essentially looking for a therapeutic agent that will block this repair process. So far two compounds have been isolated that they believe will accomplish that goal and suppress ovarian cancer stem cells. While the data to date are in vitro and animal data, the next stage will be Phase 1 clinical trials.


SELECTED KEY PUBLICATIONS 2009-2010


Faculty in the Reproductive Physiology Group investigate the physiological processes that regulate reproductive tract function. These studies range from the cellular and molecular level to clinical and translational research. The group strives to better understand the etiology and regulation of diseases of the reproductive tract with the objective of developing novel treatments and interventions. Interests include elucidation of aberrant signaling pathways in polycystic ovarian syndrome, the etiology and regulation of endometriosis, biochemical regulation of ovarian and corpus luteum function, the mechanism of embryo implantation, the development of the urogenital tract, uterine stem cells and the endocrine regulation of reproductive tract gene expression. In particular we investigate the regulatory control of sex hormones in male and female reproduction, with special emphasis on the reproductive tract during the estrous/menstrual cycle and pregnancy.

Another area of active investigation focuses on the adverse effects of environmental contaminants in a variety of human and animal models. Basic questions regarding the underlying regulation of gonadal function, such as steroidogenesis, cell proliferation and apoptosis, are also under investigation. Working with whole animals as well as at the cellular and molecular levels, studies utilize human and rodent tissues to elucidate how hormones interact with receptors and how these interactions affect differentiation, growth and cell-cell communication in the reproductive tract.

The etiology of endometriosis, adenomyosis, leiomyomata, pelvic organ prolapse, implantation failure and pregnancy loss are all studied at the
molecular, cellular and clinical levels. Novel treatments including gene therapy and stem cell therapy are under active investigation. Clinical trials in the area of menopause and polycystic ovarian syndrome are currently in progress. The research conducted within this group is supported by the NIH through several R01s, two K awards and other foundation grants. Additionally, the group was recently awarded a multimillion-dollar U54 center grant to study endometrial physiology and endometriosis.

Kathleen Connell, MD, Assistant Professor kathleen.connell@yale.edu
Hongling Du, PhD, Associate Research Scientist hongling.du@yale.edu
Umit Kayisli, PhD, Associate Research Scientist umit.kayisli@yale.edu
Pinar Kodaman, MD, PhD, Assistant Professor pinar.kodaman@yale.edu
Lubna Pal, MD, Associate Professor lubna.pal@yale.edu
Nina Stachenfeld, PhD, Associate Professor nina.stachenfeld@yale.edu
Hugh S. Taylor, MD, Professor, Chief of Reproductive Endocrinology & Infertility hugh.taylor@yale.edu
SELECTED KEY PUBLICATIONS 2009-2010

Original Research Articles: 2009


Original Research Articles: 2010


The Reproductive Neurosciences Group conducts research into the mechanisms of action of peripheral hormones, including natural gonadal steroids, the xenoestrogen bisphenol-A (BPA), and metabolic and stress hormones, on the activity and diseases of the brain. (For more details on research at Yale concerning BPA, see page 67.) Several projects focus on better understanding how gonadal steroids affect cellular functions in the hypothalamus, hippocampus and prefrontal cortex. Studies are also being conducted to reveal brain signaling modalities of metabolic hormones, including thyroid hormones, the adipose hormone leptin, the stress hormones and the gut hormone ghrelin. Particular emphasis is given to determining the interaction between gonadal and metabolic hormones with the goal of better understanding malfunctions of the hypothalamus that lead to reproductive failure, obesity and type 2 diabetes. Efforts also are under way to illuminate the role of these peripheral signals in the regulation of higher brain functions and neurodegeneration.

In recent years, studies from the Group were published in several high-impact journals, including *Nature*, *Science* and *Cell*, as well as in other *Nature* and *Cell* family journals and PNAS. Our research is also frequently featured in national and international media.

Faculty:

**Sabrina Diano, PhD, Associate Professor and Director, Reproductive Neurosciences**
sabrina.diano@yale.edu

**Tamas Horvath, PhD, DVM, Professor and Chair, Section of Comparative Medicine**
tamas.horvath@yale.edu

**Xiao-Bing Gao, PhD, Associate Professor**
xiao-bing.gao@yale.edu

**Csaba Leranth, MD, PhD, Professor**
csaba.leranth@yale.edu
Bisphenol-A (BPA), a common ingredient in plastics, may have detrimental effects on fetal sensitivity to estradiol and estradiol-mediated synapse formation, according to animal studies conducted by two Yale investigators. A team led by Hugh S. Taylor, MD, professor in the Department of Obstetrics, Gynecology and Reproductive Sciences, has discovered that exposure during pregnancy to BPA causes permanent abnormalities in the uterus of offspring, including alteration in their DNA. The findings were reported in the March 2009 issue of *Journal of the Federation of American Societies for Experimental Biology.*

The study, which is the first to show that BPA exposure permanently affects sensitivity to estrogen, used two groups of mice, one exposed to BPA as fetuses during pregnancy and another exposed to a placebo. Researchers examined gene expression and the amount of DNA modification in the uterus and found that the mice exposed to BPA as fetuses had an exaggerated response to estrogens as adults, long after the exposure to BPA. The genes were permanently programmed to respond excessively to estrogen. “The DNA in the uterus was modified by loss of methyl groups so that it responded abnormally in adulthood,” said Taylor. “The gene expression was permanently epigenetically altered and the uterus became hyper-responsive to estrogens.”

Dr. Taylor found that exposure to BPA as a fetus is carried throughout adulthood. “What our mothers were exposed to in pregnancy may influence the rest of our lives. We need to better identify the effect of environmental contaminants on not just crude measures such as birth defects, but also their effect in causing more subtle developmental errors.”

Research conducted by Csaba Leranth, MD, PhD, professor of Ob/Gyn and Neurobiology at Yale, likewise casts suspicion on BPA. His team recently found that the compound abolishes estradiol-mediated synapse formation in the primate brain, even when administered at a level deemed safe by the US Environmental Protection Agency.

In a study published in September 2009 in *Proceedings of the National Academy of Sciences,* Leranth and his colleagues ovariectomized 12 female monkeys, after which three were given a four-week course of estradiol, three a course of BPA, and three both compounds. Three more were vehicle-treated controls. After a month, the controls had a low number of nerve synapses in the hippocampus and prefrontal cortex, as would be expected from an estrogen-deficient state, while the number in estradiol-treated animals was high. But in monkeys that received BPA, as well as in those that received both estradiol and BPA, the number of synapses was as low as in the control ovariectomized group. Thus, BPA had completely prevented the estradiol’s synapse-building effect. Leranth’s was the first study to produce evidence of a direct effect of BPA on the primate brain.

The results are of concern because nerve synapse remodeling is thought to be critically important to learning and memory, as well as in mood disorders. Previous research has already found adverse effects of BPA on measures of play behavior and depressive behavior in rats. Leranth is especially concerned about effects on the developing human brain. “I believe that [it is] mostly the exposure of infants and young children that could be harmful,” said Leranth.

BPA is ubiquitous, found in everything from baby bottles to the lining of food cans. Humans are constantly exposed to low levels when the chemical leaches into food and drink. Its health effects have long been controversial; in response to consumer concerns many companies have reduced their reliance on BPA in recent years, and at least one government—Canada’s—has formally declared it hazardous.

Leranth and his colleagues plan next to conduct behavioral studies in the monkeys to see whether the change in synaptic density actually affects cognitive performance and to determine whether the reduction in spine synaptic density is reversible.


Dietrich MO, Horvath TL. The role of mitochondrial uncoupling proteins in lifespan. Pflugers Arch. 2010 Jan;459(2):269-75.


SELECTED KEY PUBLICATIONS 2009-2010
MISSION STATEMENT

Our goal is to provide a strong and stimulating foundation in women's health for all students, so that these future physicians will enter their areas of specialization with a keen interest in and accurate sense of the issues that their female patients face.

Student Teaching

The Department teaches Obstetrics, Gynecology and Women’s Health to over 390 students from Yale School of Medicine and Yale’s Physician Associate Program each year.

The first-year medical school curriculum focuses on normal reproductive physiology including embryology, puberty, the menstrual cycle, human sexual response and maternal-fetal physiology. In the second year, medical students are introduced to pathophysiology and disease processes across the lifespan, starting from birth and progressing through puberty and the reproductive years, followed by menopause and aging. In the third year, medical students enter the clinical setting during a six-week core rotation in Obstetrics and Gynecology. In the outpatient setting, they participate in the care of women seeking routine gynecologic...
screening and prenatal care, contraceptive counseling and evaluation of common gynecologic problems. In the hospital, students participate in intrapartum and postpartum care as well as the care of women undergoing gynecologic surgery. In addition, each week we offer a series of well-received didactic, interactive lectures and case-based sessions. These include weekly evidence-based medicine debates on controversial topics in obstetrics and gynecology and a weekly discussion about ethical and other challenging issues in the field.

In the fourth year, we provide subspecialty electives for students interested in more focused and in-depth experiences. These include four-week rotations in Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, Gynecologic Oncology, Ambulatory Obstetrics and Gynecology, and an off-site elective at a health services clinic on a Native American Reservation in Gallup, New Mexico.

We host events throughout the year regarding Ob/Gyn as a career, research in the field and historical perspectives. Dr. Lockwood and our faculty provide comprehensive mentoring to all students expressing an interest in Ob/Gyn.

We are proud that Dr. Illuzzi’s dedication to medical education has been recognized this year by the 2010 Leah Lowenstein Award. She is also a past winner of the Yale University Bohmfalk Teaching Prize, the top university award for clinical teaching.
The primary goal of the Obstetrics & Gynecology Residency Program at Yale University School of Medicine is to train future leaders in women’s health.

### Ob/Gyn Residency Program

The Department offers a four-year ACGME-accredited postgraduate residency training program based at Yale-New Haven Hospital. There are currently 25 residents in the program, including six categorical positions per year and an additional seventh PGY-3 categorical resident. The program remains extremely competitive and continues to attract some of the top students from medical schools around the country.

![Applications for Ob/Gyn Residency](Figure 1)
Clinical and Didactic Teaching

The Ob/Gyn Residency Program is based primarily at Yale-New Haven Hospital, with additional rotations at the nearby ambulatory sites, Yale-New Haven Temple Women’s Surgical Center and Planned Parenthood of Connecticut. A dedicated team of full-time University and community faculty provides professional oversight of the educational mission of the department. For example, during Gynecology and Obstetrics Morning Report each day, faculty members review patient cases and assist the resident staff in devising clear and rational plans of management, using the principles of evidence-based medicine. An interactive computer system allows the team to review radiologic imaging studies, laboratory data and fetal heart rate tracings in real time.

Thursday afternoons are reserved for didactic teaching, during which all Ob/Gyn residents are excused from clinical responsibilities. A comprehensive Resident Lecture Series has been developed that includes lectures by full-time Ob/Gyn faculty covering all relevant topics (including obstetrics, gynecology, reproductive endocrinology, urogynecology, gynecologic oncology, pathology, and ambulatory and primary care), with a particular emphasis on evidence-based management as well as the scientific underpinning of our discipline. One hour per week is also set aside for CREOG reviews, Journal Club and professionalism.
seminars to familiarize the residents with issues relating to patient safety, effective patient communication, professional liability, insurance, risk management and ethics.

**Resident Research**

In addition to promoting clinical and academic excellence, the Ob/Gyn Residency Program requires an original research thesis for graduation. The Department has a large number of outstanding laboratories covering the entire spectrum of basic, clinical, translational and epidemiologic research in women’s reproductive health. To introduce our residents to research, the Department sends the entire PGY-1 resident class each year to the Annual Scientific Meeting of the Society for Gynecologic Investigation. Moreover, an eight-week research elective is set aside in the PGY-3 year to allow residents to complete their research projects to be presented at our annual Residents’ Research Day. These initiatives have been enormously successful, and residents are generally invited to present their research at national and international Ob/Gyn scientific meetings each year. Virtually all residents have had their research accepted for publication in highly respected peer-reviewed journals.

**ACCOMPLISHMENTS 2009-2010**

The Ob/Gyn Residency Program has enjoyed unprecedented academic, clinical and organizational growth during the past year. Among the highlights:

1. Expansion of our comprehensive two-week PGY-1 orientation at the beginning of the intern year to include hands-on training in basic obstetric and gynecologic ultrasound and electronic fetal monitoring.

2. Introduction of a suturing skills lab to teach basic surgical technique.
3. Introduction of a monthly Journal Club in which the residents critically review and critique relevant articles and discuss patient management under the supervision of a faculty moderator.

4. Utilization of a hands-on laparoscopic simulator model and a “virtual reality” computer-simulated trainer (LapSim®), both designed to teach laparoscopic surgical technique.

5. Utilization of obstetric simulation drills using the NOELLE birthing simulator to improve management decisions and communication skills in the setting of routine obstetric care as well as obstetric emergencies.

6. Expansion of minimally invasive surgical training and experience using state-of-the-art robotic technology (da Vinci Surgical System) including the regional training center in New Jersey.

7. Improvements in the Ob/Gyn Resident Library, including the addition of new textbooks, electronic educational resources and a Residency Website with links to additional online resources, reading lists and program announcements.

8. Expansion of family planning training at Planned Parenthood of Connecticut and the addition of a dedicated Family Planning session in the Women’s Center.

9. Introduction of a Continuity Team Clinic Practice model for providing basic obstetric and primary care in the Women’s Center. Patient satisfaction scores have significantly increased in response to this innovative continuity clinic practice model.
Here at Yale, we have two laparoscopic simulators to which the residents have unlimited access. The LapSim System is a remarkable teaching tool that provides residents with a wide variety of modules that simulate various laparoscopic maneuvers. These modules help our residents develop hand-eye coordination and master tasks that require both right hand and left hand dexterity. In some of the scenarios, the computer will control movement of the camera while the student operates with both hands; in others, the student is expected to control the camera and one instrument, which adds another layer of complexity. The exercises range from basic camera and instrument navigation to vessel clipping and cautery to advanced suturing.

One of the apparent disadvantages of the system is the fact that it doesn’t offer “haptic” feedback (i.e., active touch perception), so residents don’t get the tactile cues that are present when interacting with live tissue. In one sense this is an advantage because current robotic surgery equipment doesn’t let you physically feel the tissue either; you have to rely on visual cues to perform the procedure. And while lack of tactile feedback may have some drawbacks, we utilize other simulators that provide such feedback. Box trainers are set up with real laparoscopic cameras and video systems. With these systems, the residents can use the same instruments they use in the operating room and practice tasks such as cutting, suturing and knot tying on physical objects that provide haptic feedback.

Of course, there is no substitute for training in the OR. When the faculty spends time with residents in that setting, their approach is to make sure the residents learn not only the “how” but the “why.” We want them to be the experts in the room so that when their surgical nursing team does not understand the equipment or the procedure, they can explain it. With that in mind, Dr. Beth Rackow has developed a series of lectures on laparoscopy and hysteroscopy, which discusses the techniques in detail, explaining how the instruments function, and providing details on energy sources and ways to minimize complications.

One of the more challenging pieces of equipment used in gynecology is the operative hysteroscope. There are multiple components to the equipment, including a complex tubing system. The typical office hysteroscope may have only one operative channel, but the hysteroscope we use in the OR for a major operative case has the ability to cut and cauterize, has multiple attachments, and is a complicated inflow-outflow system. Many of the residents do not know how to assemble and disassemble this equipment, and one of our goals when training residents in the OR is to get them to the point where they can independently do so.

Our surgical training program excels, not only because of the simulators and OR training, but because residents are exposed to so many experts in each subspecialty (i.e., as of July 1, 2010, seven infertility surgeons, four urogynecologists and six gynecologic oncologists) performing over 2,000 major surgeries per year and an equal number of minor cases. Our community-based physicians add nearly equivalent surgical volume. The residents get exposure to some very complicated and unusual surgeries as well as the routine procedures. And because they see so many experienced surgeons performing so many gynecologic procedures, they are exposed to a wide range of surgical techniques that they wouldn’t be exposed to in many other programs; they get to see the same procedure accomplished several different ways, which helps them begin to establish their own preferred surgical techniques.
SELECTED KEY PUBLICATIONS WITH RESIDENTS AS AUTHORS 2009-2010


