Innovation in Care, Inspired Research, Exceptional Education
Innovation in Care

At the crossroads of compassionate care and clinical innovation.

2007-2008 Academic Year Report
Inspired Research

Determining the future of women’s reproductive health through scientific advancement.

Exceptional Education

Continuing our tradition of leadership excellence through recruitment, training and fellowship.
From the Chair…

I am proud to share with you our progress in the Department of Obstetrics, Gynecology and Reproductive Sciences during this past academic year. As you will note as you peruse the following pages, our Department has grown and continues to distinguish itself across all areas of our clinical, educational, and research programs. We’ve experienced unprecedented expansion of our reproductive sciences research, in spite of the contraction of federal research funding for women’s health. We have developed our resident training program 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.

Charles J. Lockwood, MD
The Anita O’Keefe Young Professor of Women’s Health and Chair

As is evident in this report, we have continued to innovate in all areas of clinical care. Each of our clinical subspecialty sections has grown impressively in volume while embarking on significant and exciting new clinical research projects. Examples of our innovation in clinical research include a new emphasis on therapeutic vaccines in Gynecologic Oncology, a comprehensive Patient Safety Program in Maternal-Fetal Medicine, a trial of a novel device addressing sexual dysfunction 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.

“We have continued to innovate in all areas of clinical care.”

Innovation in Care
We have continued to expand clinical research activities in general, as evidenced by the number and breadth of publications and presentations at professional research meetings.

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. Seven of our physicians were listed as “top docs” in their specialties in *New York Magazine’s* 2008 “Best Doctors” issue. The Department receives high marks from Yale-New Haven Hospital leadership for its attention to patient safety and for both patient and employee satisfaction through the work of its Obstetrics and Gynecology Practice Councils. Our Labor and Birth and Gynecology Services continue to garner the highest Press-Ganey patient satisfaction scores in the Hospital. It is particularly gratifying to me from these service accomplishments that we are able take patient care just as seriously as we take research and education.

Dr. Urania Magriples prepares to perform an ultrasound on a high risk patient.
All of our research groups have continued to grow their research programs despite continuing challenges in obtaining federal funding. Overall sponsored funding has grown to $13.0 million, while total NIH funding grew to $8.1 million. This level of federal funding has moved us into the top four in NIH funding among 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 scientists.

“We continue to make important discoveries in ... reproductive health research.”

Within these pages we have highlighted several of our most exciting research findings. In addition, we continue to make important discoveries in the following areas of reproductive health research:

Cancer Biology: Aberrant regulation of steroid hormone receptors; the epidermal growth factor receptor; cell signaling proteins in ovarian, breast, and uterine cancer; and novel treatments targeting the regulation of reproductive tract gene expression.

Reproductive Neurosciences: Learning and memory effects of xenoestrogens, such as the prevalent packaging compound bisphenol A (BPA); gut and peripheral hormone influences on wakefulness and excessive feeding behaviors; and estrogenic influences on synaptic function.

Reproductive Physiology: Aberrant signaling pathways in polycystic ovarian syndrome; the etiology and novel treatment of endometriosis; characterization of uterine stem cells; and the endocrine regulation of reproductive tract gene expression.
Maternal-Fetal Sciences: The interaction of uterine, placental and immune cells in the etiology and pathophysiology of preterm delivery, preeclampsia, and intrauterine growth restriction; proteomic and gene array methodologies to identify novel markers of prematurity and preeclampsia; and the role of extracellular matrix remodeling in the placenta and myometrium.

Gamete Biology: Translational control of gene expression in the mammalian oocyte and early embryos; stress and nutrition pathways controlling the growth and death rates of ovarian follicles; and paternal effects on reproductive outcome.

We continue to offer a wide variety of training programs for reproductive physician-scientists so that our current faculty’s reputation for inspired research will continue as we develop a new generation of reproductive health scientists.

Sponsored Research Funding Trends

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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 level and continue it through active mentoring of our junior and mid-level faculty. High school students from the Greater New Haven area have an opportunity each summer to participate in our 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 also offer undergraduate 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 mission in the area of education is to train the next generation of leaders in women’s health.”

As the testimonials of students illustrate, our Ob/Gyn Clerkship Director, Dr. Jessica Illuzzi, has transformed the Ob/Gyn Clerkship into one of Yale’s top-rated clinical rotations. She incorporates debate-style forums on a controversial topic in Ob/Gyn into the didactic component of the rotation, and has involved residents as mentors to the students during their time on the clinical floors.

We select talented and accomplished graduates from medical school for our outstanding and highly competitive residency program. 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 fellows routinely present their research at their respective subspecialty society’s annual meeting 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. We currently train one AAOGF Scholar, a Research Scientist Development Program (RSDP) Scholar, a Clinical and Translational Science Award (CTSA) Scholar, and three Women’s Reproductive Health Research K12 Scholars.
OBSTETRICS SERVICE

Electronic Order Entry System
The Obstetrics service led the way at YNHH in 2008, initiating the Hospital’s new electronic order entry system. This new system uses standardized order sets for labor and postpartum as well as common conditions like preterm labor, PPROM and preeclampsia. The use of these order sets and protocols is another step in the effort to reduce medical errors and improve safety. Obstetrics continues to forge ahead with computerized medical records by serving as the first service to begin computerized patient documentation at YNHH.

Labor Floor Expansion
With the dramatic national rise in cesarean rates hitting close to home, we have devoted enormous effort to increasing Labor Floor operating room capacity through increased efficiency and better distribution of cases throughout the week. Despite a stable overall delivery volume, the increase in cesareans has resulted in a dramatic increase in maternity average length of hospital stay, causing a commensurate increase in average daily census. Noting that 80% of patients are discharged in the mid or late afternoon, we have begun to encourage a policy of 11 AM discharges for appropriate patients. By implementing patient and provider education regarding this effort, we have already noted a doubling in discharges before 11 AM.

Yale-New Haven Hospital Services

Also, to improve efficiency in the triage and disposition of our patients, we have added a midlevel obstetrical practitioner to our team. In collaboration with the health care team, our nurse practitioner provides continuity of care to antenatal patients in the triage unit through comprehensive assessment, intervention, evaluation and subsequent discharge to home or admission to the Labor and Birth unit.

New Medical Director for Labor and Birth
Positive change has also come with the addition of a new dedicated Medical Director for Labor and Birth, Dr. Christian Pettker. Dr. Pettker has been at Yale since beginning his fellowship in Maternal-Fetal Medicine in 2004. With clinical interests in medical complications of pregnancy and the management of labor and delivery, he is well suited to direct our medical services on this unit. Moreover, Dr. Pettker’s research interests relate to...
clinical and outcomes-based research, particularly in labor and delivery. With Dr. Edmund Funai, he has worked on developing and studying the comprehensive patient safety program at Yale, which has demonstrated significant reduction in obstetrical adverse outcome rates. His work continues to focus on patient safety efforts as well as risk/adverse outcome perception in obstetrics.

**Patient Safety Emphasis**
The Obstetrics Service has continued to improve upon its safety initiatives introduced over the past two years. Patient safety is the top priority for each physician, nurse, resident and fellow. Our commitment to patient safety has resulted in a steady decline in preventable adverse obstetrical events and, as noted above, patient safety is not only an operational priority for our new Director of Labor and Birth, but also a clinical research emphasis.

**GYNECOLOGY SERVICE**

*Inpatient Gynecologic Care at Yale-New Haven Hospital*
The inpatient unit increased its bed capacity from 28 to 32 beds over the last year to accommodate increasing volume. In order to maintain a high standard of care to address this volume, we created an additional midlevel practitioner position. The unit currently has one Physician Assistant, who is available on the unit four days per week. She is responsible for ensuring safe, high-quality care for inpatient gynecology/oncology patients. This position has contributed to significant increases in patient and staff satisfaction,
as she is able to respond quickly to the needs of patients and families. We identified further needs on the evening shift when many patients arrive on the floor from the recovery room. The addition of a second midlevel position will allow the same high level of care to extend into the evening shift.

The inpatient service has made tremendous efforts to address patient satisfaction. The inpatient unit has consistently maintained a Press-Ganey Patient Satisfaction survey score in the high 90s, with the outpatient gynecologic oncology practice and its chemoinfusion suite consistently scoring in the 90s. In an effort to improve the care delivered to gynecologic oncology patients, we created an “In/Out” forum. This is a weekly meeting including an inpatient and outpatient RN, the assistant manager of the inpatient unit, the outpatient PA, the inpatient PA, the social worker for the service, the chaplain, the care coordinator and the palliative care APRN. The purpose of the meeting is to discuss patients who have been discharged, as well as patients who will be admitted, to ensure that everyone has a clear understanding of the plan for the patient; we also discuss outstanding issues and clinical challenges. The improved and regular communication has contributed to seamless care between the inpatient and outpatient settings as well as improved staff satisfaction.

In the spring of 2008, members of the gynecologic oncology nursing staff presented two posters at the Society for Gynecologic Nurse Oncologists annual meeting in Denver, Colorado. The abstracts were entitled: “Improving Patient Satisfaction – Creating a Spa Experience” and “Preparing Patients for Platinum Desensitization.” Meeting members from throughout the US and Canada received both posters enthusiastically.

**Departmental Quality & Safety**

The Gynecology Service is dedicated to high-quality, safe patient care. To improve the safety of care delivered to our patients, we implemented the following initiatives:

- The Gynecology Practice Council, an interdisciplinary group, meets monthly to monitor and implement initiatives focused on quality and safety. Over the last year, the Council has had goals related to the following safety and quality measures: appropriate documentation of time-out and consent procedures, timely administration of antibiotics perioperatively, standardization of venous thromboembolism prophylaxis and timeliness of chemotherapy order entry.
• We developed a standard operating procedure related to elective chemotherapy admissions. This procedure mandates that chemotherapy orders be entered 24 hours in advance of admission or treatment date. This time line allows adequate time for nursing and pharmacy staff to review the orders and ensure accuracy, minimizing treatment delays for the patient. This effort has increased the timeliness of treatment, thereby improving patient satisfaction.

• We have instituted a policy mandating that all nurses who administer chemotherapy attend the national Oncology Nursing Society Chemotherapy and Biotherapy Class, maintain the ONS chemotherapy provider card status by renewal every two years, and attend an annual hospital-based recertification. These efforts ensure that all oncology nurses are learning the same content and are held to the same safety standards.

• In an effort to improve the safety of chemotherapy order entry, the Oncology Pharmacist and the Oncology Clinical Nurse Specialist review and track all errors, including near misses related to chemotherapy, and provide regular feedback to the prescribers and the Gynecology Practice Council. In addition, a number of systems changes have been made to decrease the opportunity for error.

• We created a comprehensive carboplatin desensitization program including a standard of care, treatment algorithms, skin testing procedures and patient education materials. All Gynecologic Oncology nursing staff completed an educational competency course related to the desensitization process. The Service has since successfully delivered over 100 desensitizations.

• A practice guideline, competency and order set for the administration of intraperitoneal chemotherapy was also developed in response to the emerging literature demonstrating improved outcomes in carefully selected patients.

Luisa Coraluzzi, BSN, monitors a study participant’s vital signs.
Maternal-Fetal Medicine

Edmund F. Funai, MD
Associate Chair for Clinical Affairs, Section Co-Chief and Chief of Obstetrics at Yale-New Haven Hospital, Associate Professor
Interests: Long-term consequences of preeclampsia, premature birth, perinatal patient safety

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

Joshua A. Copel, MD
Vice Chair of Obstetrics, Director of Ob/Gyn Ultrasound, Professor
Interests: Prenatal diagnosis, fetal echocardiography, fetal therapy

Urania Magriples, MD
Associate Professor
Interests: Infectious disease, HIV, models of prenatal care delivery

France Galerneau, MD
Associate Professor
Interests: Prenatal diagnosis, medical education

Michael J. Paidas, MD
Co-Director, Yale Women and Children’s Center for Blood Disorders, Associate Professor
Interests: Thrombosis and hemostasis in pregnancy and adverse pregnancy outcome

Catalin S. Buhimschi, MD
Assistant Professor
Interests: Translational and proteomic research, preterm birth, myometrial physiology and healing

Mert Ozan Bahtiyar, MD
Director of the Fetal Surgery Program, Assistant Professor
Interests: Prenatal diagnosis, fetal echocardiography, fetal surgery, perinatal epidemiology

Errol R. Norwitz, MD, PhD
Obstetrics and Gynecology Residency Program Director, Maternal-Fetal Medicine Fellowship Program Director, Section Co-Chief, Professor
Interests: Molecular mechanisms of parturition at term and preterm, genomics of prematurity

Stephen F. Thung, MD
Yale Maternal-Fetal Medicine Practice Director, Director of the Yale Diabetes Management During Pregnancy Program, Assistant Professor
Interests: Diabetes, infectious disease, HIV, preterm birth prevention

Anna K. Sfakianaki, MD
Director of Gynecologic Ultrasound, Assistant Professor
Interests: Premature birth, progesterone supplementation, perinatal epidemiology

Heather S. Lipkind, MD, MPH
Assistant Professor
Interests: Perinatal epidemiology, environmental insults and adverse pregnancy outcome

Christian M. Pettker, MD
Medical Director, Labor and Birth, Assistant Professor
Interests: Clinical research, preterm birth, perinatal epidemiology, perinatal patient safety

Ashley S. Roman, MD, MPH
Assistant Director of Perinatology at Greenwich Hospital, Clinical Assistant Professor
Interests: Prenatal diagnosis

For full bios of our Maternal-Fetal Medicine physicians, please visit http://yalehighriskpregnancies.org/physicians.html.
OUR PHILOSOPHY AND MISSION

The primary mission of the Section of Maternal-Fetal Medicine is to provide specialized care for women with high-risk pregnancies. In addition, the Section strongly emphasizes resident and fellow education, and promotes and supports innovative research with a view to improve patient care and pregnancy outcomes.

Education and Training

An equally important mission of the Section is to educate and train Ob/Gyn residents, Maternal-Fetal Medicine fellows and Yale medical students. 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 Maternal-Fetal Medicine faculty are responsible for a comprehensive series of didactic sessions on pregnancy-related complications.

The three-year, highly competitive Maternal-Fetal Medicine 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. A significant amount of time (18 months) is set aside specifically for research with a view toward training physician-scientists and future academic leaders in the field of Maternal-Fetal Medicine.

The Section of Maternal-Fetal Medicine 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 Maternal-Fetal Medicine consists of 14 attending physicians and seven 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 involve couples actively 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 hundreds of transfers to our outpatient high-risk practice for consultation or ongoing care.

• Comprehensive genetic counseling and testing. Our innovative program offers “instant” 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 surgical procedures that require specialized training.

• Management of complex diabetes cases before, during and after pregnancy.

• Comprehensive gynecological ultrasound services for general Ob/Gyn providers and gynecologic oncologists.

Research
The research mission of the Maternal-Fetal Medicine Section is to coordinate and conduct high-quality basic science, clinical, epidemiologic and translational research in a safe environment for investigators and patients. The Section uses state-of-the-art technology (Doppler, mass spectrometry, micro-array, functional MRI) to accomplish these goals.

Accomplishments 2007-2008
The Section of Maternal-Fetal Medicine enjoyed unprecedented academic and clinical growth during the past year. Among the highlights:

1. Given the favorable environment for academic medicine in the Yale Maternal-Fetal Medicine Section and despite the current shortage of Maternal-Fetal Medicine specialists around the country, the Section continues to maintain an impressive cadre of 14 faculty 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 various national and international scientific conferences. The Section was second among all U.S. medical schools in presentations at the 2008 Society for Maternal-Fetal Medicine Annual Scientific Meeting in Dallas. In total, the Section had six oral presentations, two of which won awards for best presentation, and 23 poster presentations. A similarly impressive performance was evident at the 2008 Society for Gynecologic Investigation meeting in
San Diego, CA (two oral presentations and 19 poster presentations) and the 2008 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 techniques and tools available at the University for use in future clinical studies.

3. National influence: The Section continues to have faculty in leadership positions in national organizations. Charles Lockwood was designated President of the Society of Gynecologic Investigation while Joshua Copel continues his role as President of the American Institute of Ultrasound in Medicine. 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. Continued commitment to education: The Maternal-Fetal Medicine Section offered the First Annual Yale Obstetrics/Gynecology Update, a CME course at Mohegan Sun Resort. A variety of “hot” topics in Perinatology and Obstetrics were discussed with participants from all over the country.

Dr. Joshua Copel discusses the results of an ultrasound scan with a patient.

5. The Maternal-Fetal Medicine clinical service continues to grow robustly:
   a. Ultrasound volume has steadily increased, up 138% since 2002 with over 28,000 scans performed annually.
   b. The First Trimester Down Syndrome Screening Program continues to expand, with over 300 visits per month.
   c. The number of diabetes cases managed by the Section increased 85% from 2005 for a total of 275 cases in 2007.
   d. Total clinical revenue has steadily increased every year, now up 165% since 2002.

Goals 2008-2009

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 and preeclampsia.

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 room and general Ob/Gyn practices.

5. To 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.

Selected Key Publications (of 61 for the academic year):


Staff members at our outpatient clinical practice site focus on providing excellent customer service.
MATERNAL-FETAL MEDICINE’S SPECIAL EMPHASIS ON PATIENT SAFETY

Perinatal Safety

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. 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 by nonsubscribers.

We continue a trend of decreasing quarterly adverse outcomes in our obstetrical services (see figure at left) 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 services.

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?’”
Reproductive Endocrinology and Infertility

Hugh Taylor, MD
Section Chief, Professor
Interests: Infertility, reproductive surgery, congenital anomalies of the uterus, DES exposure, implantation/endo- metrial 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

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

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

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 or oncological treatment

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

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

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

Pinar Kodaman, MD
Co-Director, Yale Recurrent Pregnancy Loss Program, Assistant Professor
Interests: Polycystic ovarian syndrome, recurrent pregnancy loss, reproductive surgery and infertility

For full bios of our Reproductive Endocrinology and Infertility physicians, please visit http://yalefertilitycenter.org/physician/index.html.
OUR PHILOSOPHY AND MISSION

The mission of the Section of Reproductive Endocrinology and Infertility is to provide specialized care for women and men with a variety of reproductive endocrine disorders and infertility, to conduct 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.

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 Fellowship Program in Reproductive Endocrinology and Infertility 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 fellow gains 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,

Yale Fertility Center IVF Cycle Growth Trend

![Yale Fertility Center IVF Cycle Growth Trend](image-url)
our physicians are expected to become independent leaders in the practice and advancement of the specialty.

Clinical Services

Our Section’s 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.

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 existing 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 on fertility. Novel treatments such as aromatase inhibitors for ovulation induction, low-dose hormone therapy for menopause, several novel treatments for endometriosis, new methods of embryo evaluation and selection, and ovary/oocyte freezing are currently under study.

Accomplishments 2007-2008

1. 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 57%.

2. We experienced growth of over 4% in total clinical volume.

3. We expanded our Oocyte Cryopreservation Program established two years ago (under IRB 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. Lubna Pal and Pinar Kodaman. Dr. Pal heads our Clinical Research Program, studying polycys-
tic ovarian syndrome and menopause. Dr. Kodaman is a distinguished Women’s Reproductive Health Research (WRHR) Scholar who is also studying the potential role of statins in treating PCOS.

5. We recruited a highly regarded IVF laboratory manager with 20 years of experience in the field of embryology.

6. 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.

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

Yale Fertility Center 2007 IVF Pregnancy and Live Birth Success Rates

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<td>40</td>
<td>10.0</td>
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Goals 2008-2009

1. Increase the number of IVF cycles by 10%.
2. Increase third party reproduction (oocyte donation and gestational surrogacy) cycles by 25%.
3. Grow the Egg Freezing Program by 20%.
4. Create a new Egg Donor Bank service.

5. 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.

6. Increase male infertility visits and surgeries by 10%.

7. Expand the clinical practice by opening an office in Fairfield County.

Selected Key Publications (of 50 for the academic year):


### The Yale PCOS Program: A “One-Stop Shop” for Women with PCOS

Because polycystic ovarian syndrome (PCOS) affects more than just the ovaries, Yale experts are teaming up to form a PCOS center for excellence. Clinicians at the Yale PCOS Program will not only treat PCOS but also address problems that may accompany this diagnosis, including fertility problems, body weight and body image issues, high cholesterol, insulin resistance and risk for diabetes, high blood pressure and risk for heart disease. The result will be what Dr. Pinar Kodaman, Program physician, calls a “more holistic approach.”

“Beyond improving the overall health of women with PCOS, our goals are to help patients take charge of PCOS,” says Dr. Lubna Pal, director of the Yale PCOS Program. During a single convenient appointment, patients will undergo evaluation by our team of expert practitioners. Management strategies will be individualized to the needs of each patient. Risk profiles for heart disease and diabetes will be determined through detailed assessments, including tests that reflect the most advanced research into the disorder. Health goals will be identified (target weight, cholesterol, blood pressure, blood sugar, vitamin D level) and our team will work with each patient to ensure that these goals are met.

Sophisticated and individualized management strategies will address PCOS-related infertility to ensure that fertility treatment-related risks (such as ovarian hyperstimulation syndrome and multiple pregnancy) are minimized. Utilizing sophisticated and individualized treatment plans, the Yale PCOS Program will strive to achieve healthy pregnancies in healthy mothers.
Each of the Yale Ob/Gyn practitioners at the Yale PCOS Program brings special expertise to the table:

- Adolescents and teenagers with symptoms of PCOS (such as menstrual irregularities, excessive facial and body hair and acne) will benefit from Dr. Beth Rackow’s expertise in adolescent gynecology and menstrual disorders.

- Utilizing combinations of lifestyle modifications and medications, Dr. Kodaman will focus on reducing risks for cardiovascular disease while Dr. Pal concentrates on issues of insulin resistance and diabetes.

- Dr. Stephen Thung, a Yale Maternal-Fetal Medicine specialist with a special interest in the management of diabetes and hypertension in pregnancy (common in women with PCOS), joins the team as a resource for preconception consultation for patients deemed at high risk for pregnancy-related problems.

- Amy Krystock, a registered dietitian, employs a total lifestyle modification approach, utilizing customized diet and exercise programs for women with PCOS.

- Dorothy Greenfeld, LCSW, provides an invaluable resource for psychological support, helping patients overcome the stress of PCOS symptoms and diagnosis.

By combining our efforts and expertise, we hope to be able to address the health needs of women of all ages diagnosed with PCOS. “I can foresee a teenager with PCOS being cared for at our center through her reproductive years into menopause,” says Dr. Pal.

EXPERTISE FOR CHILDREN WITH GYNECOLOGIC DISEASE

When faced with a prepubertal girl who needs a speculum exam, many gynecologists might feel uncertain. But age-appropriate gynecological exams for children are a special emphasis for Beth W. Rackow, MD, assistant professor of obstetrics and gynecology. Her practice emphasizes pediatric and adolescent gynecology, the only one in southern Connecticut to do so. In addition to her adult academic practice, she sees teenagers and children as young as three.

Such young children may be referred for vaginal discharge, prepubertal vaginal bleeding or labial adhesions. Older children and adolescents commonly see Rackow for primary or secondary amenorrhea, dysmenorrhea, pelvic pain, or abnormal or irregular menstrual bleeding. She also cares for patients with imperforate hymen and anomalies of the reproductive tract, including vaginal and uterine anomalies. Rackow estimates that she operates on about one-quarter of these anomalies.

General indications to refer to a pediatric gynecologic subspecialist include the need to do an exam under anesthesia, the need to discuss complex reproductive topics with children and parents, and problems requiring experience with unusual pathologies, including surgical experience. “I am not there to do first gynecologic exams [or] STD screenings,” says Rackow. “I prefer the problems:"

Rackow says she became comfortable with pediatric and adolescent gynecology during her reproductive endocrinology training, but she also worked for an intensive month with S. Paige Hertweck, MD, Director of Pediatric and Adolescent Gynecology, University of Louisville, Kentucky. She participates in clinical research and maintains contact with mentors around the country.
**Our Philosophy and Mission**

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 horizon of care for women with gynecologic cancers. We employ a multidisciplinary approach to comprehensive management of gynecologic malignancies and offer clinical trials participation as a member of the Gynecologic Oncology Group for national cooperative study group trials and multiple pharmaceutical, physician-sponsored trials. We have a very active early detection and prevention program for ovarian cancer. Each physician emphasizes a minimally invasive approach to gynecologic cancer, 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 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 2007-2008
1. Clinical volume continues to increase. We currently have outreach programs in 10 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 400 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. Our Section recruited two new gynecologic oncologists this year.
3. Our Section sponsored the 24th Ella T. Grasso Memorial Conference this year, along with the fourth annual Discovery to Cure Gala and first annual walk for ovarian cancer.

Goals 2008-2009
1. Recruit new faculty to develop new research thrusts that are compatible with our current programs, as well as support expansion of our outreach services.
Selected Key Publications (of 16 for the Academic Year):


TRAINING THE IMMUNE SYSTEM TO FIGHT RECURRENT CERVICAL CANCER

Cervical cancer is often successfully treated in its early stages with surgery and radiation, but if it recurs—as it does in up to one-fifth of even those patients with negative lymph nodes at initial treatment—the prognosis is poor. Alessandro D. Santin, MD, professor of obstetrics and gynecology, hopes to develop a vaccine to prevent and treat recurrences. “What we would like to do is to offer this new form of vaccination after the gold standard therapy,” he said. (Gardisil, the recently approved HPV vaccination aimed at girls and young women, is intended as a preventive vaccine, not as therapy for those already infected by the virus.)

In a phase I study published recently in the Journal of Virology, Santin and his colleagues harvested dendritic cells (DC) from 10 women with stage IB or IIA cervical cancer who had already undergone surgical treatment. The team loaded the cells with full-length recombinant E7 HPV antigen, a transforming oncoprotein found in high-risk HPV types, and then reinjected the patients with their own primed, mature dendritic cells. All 10 patients demonstrated an immune response to E7 in a non-dose-dependent fashion, while none experienced any toxicity. Further, although the study was not designed to examine clinical response, routine follow-up has detected no recurrence of the cancer in any of the study subjects over a three-year period.

The team examined several measures of immune response. Antibody titers rose in all 10 patients relative to baseline—some de novo, others as a magnification of preexisting antibodies—while skin reactions indicated that delayed-type hypersensitivity had developed. When interferon-gamma (IFN-γ) secretion was measured as an indication of Th1 activation in CD4+ and CD8+ T-cells, all 10 patients’ IFN-γ-secreting CD4+ cell frequencies rose compared with baseline in reaction to both E7 and the immunogenic keyhole limpet hemocyanin (KLH) vehicle. CD4+ Th1 cells are essential to the process of developing cytotoxic immune responses.

Seven patients showed a corresponding rise in IFN-γ-secreting CD8+ cell frequency in reaction to E7 (they did react to KLH), although the median ratio compared with baseline did not reach statistical significance. The authors speculated that the failure of the CD8+ counts to rise more robustly, when they did so in a previous trial, may be attributable to differing loading techniques.

Dendritic cells are potent antigen-presenting cells that are crucial for activating both CD4+ and CD8+ T-cell immune responses to antigens, and previous studies have found that DC-based vaccines can cause regression of metastases in some patients with lymphoma and melanoma.

Santin next plans to conduct a phase II trial of the vaccines in a similar patient population, this time with clinical outcomes measurements. It will also take into account tolerogenesis, a phenomenon wherein cancer cells induce tolerance in the immune system and an insufficient clinical response in some patients to autologous vaccines. When vaccinating a cancer patient, Santin said, “You are not vaccinating a normal individual—you are vaccinating a patient who already has a lot of tolerogenic CD4+ T-cells in the peripheral blood.” Small doses of chemotherapy may be effective in clearing tolerogenic cells before vaccination takes place.

The immune system’s potential power to destroy cancerous tissue, Santin pointed out, is amply demonstrated by the dramatic phenomenon of solid organ allograft rejection. “But,” he said, “it needs to be directed properly.”
Richard Bercik, MD
Assistant Professor, Section Chief, Urogynecology and Reconstructive Pelvic Surgery
Interests: Diagnostic and treatment modalities for problems of urinary and fecal incontinence, pelvic organ prolapse, pelvic floor disorders, interstitial cystitis, single and multi-channel urodynamic testing, anal manometry, office cystoscopy, biofeedback for urinary and fecal incontinence, advanced laparoscopic surgery, abdominal and pelvic floor reconstruction, vaginal hysterectomy for the enlarged uterus, vaginal fistulae, minimally invasive surgery for prolapse and incontinence

Kathleen Connell, MD
Assistant Professor, Director of Research, Urogynecology and Reconstructive Pelvic Surgery
Interests: Diagnostic and treatment modalities for problems of urinary and fecal incontinence, pelvic organ prolapse, pelvic floor disorders, interstitial cystitis, single and multi-channel urodynamic testing, anal manometry, office cystoscopy, pelvic floor muscle rehabilitation and biofeedback for urinary and fecal incontinence, advanced laparoscopic surgery, abdominal and vaginal pelvic floor reconstruction, incontinence procedures, vaginal fistulae

Marsha K. Guess, MD, MS
Assistant Professor
Interests: Vaginal and abdominal pelvic reconstructive surgery, advanced laparoscopic (minimally invasive) surgery, transurethral collagen injections for pelvic floor disorders, pelvic organ prolapse, sexual dysfunction

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, urodynamic studies, cystoscopy, rectocele, cystocele, sexual dysfunction

For full bios of our Urogynecology and Reconstructive Pelvic Surgery physicians, please visit http://yaleobgyn.org/urogyn/physicians.html.
OUR PHILOSOPHY AND MISSION
We endeavor to provide the best possible care for our patients in an environment of respect, compassion and concern. Best care in our Section means not only choosing a treatment with the highest long-term cure rate with low associated morbidity that best meets the patient’s goals and expectations, but also that the patient is accurately informed about all of her treatment options.

Furthermore, our Section strongly emphasizes resident education, community outreach and innovative research to improve the care of those patients with Pelvic Floor Disorders (PFD).

Education and Training
Residents continue to participate fully in the Section’s clinical practice where they learn to evaluate women with urinary and fecal incontinence, uterovaginal prolapse and other PFD. They are introduced to appropriate non-surgical and surgical treatment modalities. Several residents are actively involved in clinical and basic research projects, and two of the six graduating residents have been accepted into fellowship training in our subspecialty. Gynecologic surgeons visit regularly to observe recently developed surgical techniques.

Clinical Services
Our faculty members have advanced training in managing disorders of the female pelvic floor and offer evidence-based treatment options for women afflicted with pelvic organ prolapse, urinary and fecal incontinence, interstitial cystitis and pelvic floor fistulae.

Our facility provides state-of-the-art diagnostic equipment and evidence-based treatment options for women afflicted with problems of PFD including:

- Comprehensive evaluations of PFD
- Single and multi-channel urodynamic testing
- Office cystoscopy
- Pelvic floor muscle and neurodiagnostic evaluations
- Pelvic floor rehabilitation with biofeedback and electrical stimulation
- Myofascial release technique for dyspareunia
- Transurethral and paraurethral collagen injections
- Office testing for spinal neuromodulation
- Minimally invasive surgical options
- Anal manometry
- Advanced vaginal, laparoscopic and abdominal reconstructive pelvic surgeries
Research
NIH-funded research includes 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. Clinical trials to investigate non-medical treatments for female sexual dysfunction have been initiated. We will soon begin enrolling patients into a randomized surgical trial investigating the use of vaginal mesh in prolapse repair.

Accomplishments 2007-2008
2. Identified as one of the top five practices in the Yale Medical Group for patient satisfaction for the year.
3. 35% increase in new patient visits and 20% increase in major surgical repairs.
4. Increase in clinical revenue of 15% despite declining reimbursements.
5. New treatment modalities have been added, including office placement of spinal leads for spinal neuromodulation for recalcitrant overactive bladder.
6. Phase II Interstim Neurostimulator Therapy with postoperative programming done in the office by our nurse practitioner.
7. Cherrilyn Richmond, our nurse practitioner, is a part-time faculty member of Yale School of Nursing and has begun instruction of NP students, both in the classroom and with clinical preceptoring.
8. We have recruited a fourth faculty member to allow for expansion of clinical and research activities.
9. Secured ABOG accreditation for the fellowship.

Goals 2008-2009
1. Continue research into genetic and molecular causes of pelvic floor disorders with presentation and publication of these important results.
2. Increase NIH funding by successful application for continued funding.
3. Expand outreach program with our affiliated hospitals.
4. Expand our geographical presence for patient care.

Selected Key Publications:

Connell KA, Guess MK, Tate A, Andikyan V, Bercik R, Taylor HS. Vaginal Expression of HOXA13 is diminished in women with pelvic organ prolapse, Menopause (2008); In press

GOOD OSCILLATIONS: A VIBRATOR THAT MAY HELP WOMEN WITH SEXUAL DYSFUNCTION

Female sexual dysfunction is a poorly understood disorder that may include problems with libido, arousal, orgasm or pain during sex. Marsha K. Guess, MD, assistant professor of obstetrics and gynecology, is about to launch a study to determine whether a new twist on an old-fashioned device—the vibrator—may help some women with sexual dysfunction improve their sexual satisfaction.

Unlike male sexual dysfunction (SD), which in many cases is known to stem from organic causes, female SD is still often considered a psychological phenomenon. “If you go back 60 years, SD in men was thought to be due to psychological causes,” says Guess. “But after researchers realized that many cases of male SD were organic, treatments were developed.” Guess expects that a similar change will occur in the approach to treating female SD with a better understanding of the etiologies of the disorder through research. She is among several investigators to have described a phenomenon of diminished genital vibratory sensation among apparently healthy women with SD. That led her to wonder if SD is a neurological problem and, if so, whether it is permanent or if it can be overcome.

Guess and her colleagues will soon study a currently marketed device similar to a vibrator. This device is different in that it oscillates rather than vibrates. They will investigate whether a baseline deficit in genital sensation that has led to SD can be compensated for by the heightened stimulation the device provides. About 80 healthy women with self-reported problems with arousal and/or orgasm will participate. After undergoing a baseline measurement of genital vibratory sensation, they will use the device at will, keep a sexual response diary, and complete validated questionnaires at one and three months to assess their sexual satisfaction. A secondary endpoint will be whether genital sensation changes over time.

Guess believes the device may have an advantage over conventional vibrators because this device provides intense stimulation without desensitization. “If your vibrator stops functioning, you may not have a good experience,” she says. “When we heard about [this device], we all thought that this device might really make a difference for some women.”

Female sexual dysfunction is thought to afflict some 20% to 50% of American women, but satisfactory treatments are still elusive. The only FDA-approved treatment—a suction apparatus called the EROS Clitoral Therapy Device—may not be ideal for all women, since it works by augmenting diminished blood flow, a problem that may not affect all women with SD. Testosterone has also been tried, with mixed results. “Some of the lack of enthusiasm in female SD is due to the lack of treatment options,” says Guess. “It’s hard to get people excited about participating and talking about the problem if there is no treatment for the disorder.”

Guess hopes that future studies will compare the oscillating device to other vibrators. “If we find some benefit, it might encourage more people to seek care…and stimulate interest in funding research projects to look at the problem more closely,” says Guess. “These treatment options may work, but we’re just at the tip of the iceberg…There will be many more questions yet to be answered.”
Susan Richman, MD, MPH
Section Chief through 2007-2008 academic year, Assistant Professor
Interests: Family planning, vulvodynia, sexuality

Anna K. Sfakianaki, MD
Director of Gynecologic Ultrasound, Assistant Professor
Interests: Family planning, gynecologic ultrasound

Christian M. Pettker, MD
Assistant Professor
Interests: Family planning, clinical research, perinatal epidemiology

Beth W. Rackow MD
Assistant Professor Ob/Gyn & Pediatrics
Interests: Family planning, ESSURE, PCOS, office-based permanent contraception

Family Planning

OUR PHILOSOPHY AND MISSION
The Section of Family Planning provides specialized care for women with reproductive planning needs. In addition, our Section strongly emphasizes resident education and innovative research to improve patient care 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 their advantages and disadvantages.

An important mission of our Section is to educate residents about our subspecialty. Second-year residents can elect a seven-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. 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. We believe that the knowledge and surgical skills gained from these activities will allow our residents to evaluate and manage a wide range of office gynecologic issues, such as threatened or incomplete miscarriage, menorrhagia and dysfunctional uterine bleeding.
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 pathophysiologic mechanisms 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/experience in contraceptive counseling, provision of all currently available methods, and observation of professional counseling sessions with the staff. 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.

**Accomplishments 2007-2008**

The Section of Family Planning continued its academic and programmatic growth during FY 07-08 as demonstrated by the following:

1. Continuation of collaborative clinical rotation for PGY2 residents at the New Haven Planned Parenthood site.

2. Improved and expanded lecture series in family planning-abortion services.
3. Continued growth of Yale Family Planning as a referral practice for genetic/structural terminations, contraception services and vulvodynia.

4. Collaborative investigation of the safety and tolerability of a novel non-hormonal vaginal contraceptive ring.

Goals 2008-2009

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.

Selected Key Publications


COMPASSIONATE AND PROFESSIONAL CARE FOR ABNORMAL PREGNANCIES

A young, recently married couple was surprised when they conceived twins that would be due on their first anniversary. Their obstetric care provider arranged first trimester screening at our MFM Long Wharf facility. Abnormal ultrasound findings led to chorionic villus sampling, which tragically revealed that both twins were affected by trisomy 18, a chromosomal defect that uniformly leads to early neonatal death.

After extensive counseling by Perinatal Genetics and consultation with Pediatrics, the decision was made to refer the family to Family Planning. Swift arrangements were made for an operative delivery in ambulatory surgery. In the recovery area, YNHH pastoral counseling provided support for the grieving parents and their extended family, and the fetuses were baptized on site.

The Hygeia Foundation offered an opportunity for the couple to share stories and poems written by other families who had experienced similar losses.

At her one-week postoperative visit, the patient freely expressed her gratitude for the “compassion heaped upon” her by everyone in the chain of care: providers, secretaries, counselors and nurses. She felt “immediate trust and confidence in the skills of each.” Acknowledging this as the most devastating emotional situation she had ever faced, and realizing that intrusive dreams were disrupting her ability to sleep, she accepted care from a YSM professional specializing in women’s mental health. A combination of talk therapy and medication has allowed her to return to work and courageously plan a second pregnancy as soon as possible.
GAME BIOLOGY RESEARCH GROUP

The Gamete Biology Research Group is comprised of six internationally recognized researchers whose laboratory projects span translational research with direct clinical implications to basic molecular investigations into gene expression in embryos and gametes. Research emphases fall into the following categories:

**Female Reproduction:**
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 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 pathways control the growth and death rates of ovarian follicles that contain egg cells.

**Male Reproduction:**
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.

**Preimplantation Embryo Development:**
1) Non-invasive assessment of embryo viability in assisted reproduction; 2) Preimplantation Genetic Diagnosis and investigation of novel techniques of screening for aneuploidy in single blastomeres; 3) Characterizing the gene expression profiles of human embryos and gametes; and 4) Assessing the developmental capacity and growth patterns of normal and abnormal embryos.

**Gonadal Development:**
1) Gonad development in the fetus and 2) Developmental establishment of stem cell “niches,” or compartments, that support the developing and adult ovary.

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Selected Key Publications (of 28 for the academic year):


Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril.* 2007 Dec;88(6):1568-72.

Dr. Maria Lalioti demonstrates a technique to colleagues in the Gamete Biology Group.
GENES MAY AFFECT THE SUCCESS OF IVF

Patients undergoing in vitro fertilization may respond in very different ways to the same dose of follicle-stimulating hormone (FSH), even when age is taken into account. Some produce only a few eggs, while others are hyperstimulated. Maria Lalioti, PhD, a geneticist in the department, has discovered splicing variants in the FSH receptor in ovarian granulosa cells that might partially explain why.

Her team recruited 29 women undergoing fertility treatment. All women were under age 35 and had had either abnormally low (<5 eggs) or high (>18) responses to a standard FSH dosing protocol. Women producing eight to 17 eggs served as controls. After extracting RNA from cumulus cells surrounding the oocytes, the team was able to isolate and characterize four splicing variants in the FSH receptor—three exon deletions and one intron insertion. (All women carrying such a variant were heterozygous for the wild-type receptor.) Markedly decreased cAMP activation, a measure of FSH effectiveness, was observed in human embryonic kidney cells and rat granulosa cells transfected with each of the four variants.

In cells co-transformed with both variant and wild-type receptor, one variant—a deletion of exon 2 associated with a low oocyte response in carriers—suppressed cAMP response, thereby exerting a dominant-negative effect that was consistent with the phenotype. Other heterozygous cells were partly responsive to cAMP.

The team also studied two wild-type polymorphisms that are associated with a slightly different response to FSH stimulation, and found that one of them produces less cAMP in response to a large dose of FSH. “In the end, you might treat [some] patients better by not giving them too much hormone,” said Lalioti.

The results, which are undergoing peer review for publication, strongly suggest an intrinsic genetic cause of some forms of subfertility. Lalioti’s presentation won an award in July of 2008 at the conference of the European Society of Human Reproduction and Embryology in Barcelona, Spain.

The FSH receptor is a G-protein-coupled transmembrane receptor with an extracellular FSH binding site. When FSH binds to the receptor, it triggers an intracellular cAMP-dependent signaling cascade that leads to estrogen production and oocyte development. Point-mutation variants in the receptor have already been described, some of which cause abnormal sexual development and loss of fertility, and others that lead to ovarian hyperstimulation during pregnancy. Exon skipping in the FSH receptor has also been described in Sertoli cells of infertile human males. However, no previous study in women has characterized these variants in women with a measurable phenotype.

The team next plans to express variant receptors in non-luteinized human granulosa cells in vitro. They also plan to further study patients with wild-type polymorphisms with the goal of tailoring the dose of FSH to the individual patient. “The ultimate aim is to know how many players [influence] the number of oocytes that are produced through this cycle,” said Lalioti. Therapeutic targets may eventually be developed downstream of the receptor itself, so that women with splice variants will not be dependent upon those receptors for a robust ovarian response to FSH stimulation.
MATERNAL-FETAL SCIENCES GROUP

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 on preterm delivery specifically seeks to dissect the mechanism through which progesterone supplementation can prevent preterm birth. Proteomic and gene array methodologies are being developed to identify novel markers of PTD and PE, which will facilitate the development of new diagnostic and therapeutic strategies. Studies 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 that is associated with IUGR.

A major focus of this group is the analysis of the interaction of uterine, placental and immune cells in the etiology and pathophysiology of PTD, PE and IUGR. Studies include the evaluation of separate and interactive effects of ovarian steroids and pro-inflammatory cytokines on the expression of members of the IL-6 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 molecular methodologies. 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.

The differential roles of placental and renal synthesis of the angiogenic factors VEGF and PLGF and their antagonist sFlt-1 in pregnancy-induced hypertension and proteinuria are under study using animal models and placental and kidney cell cultures. The specific role of hypoxia and plasmino-vascular 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. In addition, the role of tissue factor and other hemostatic regulators in abnormal uterine bleeding and endometriosis, major causes of infertility and of consultations for women, are also actively investigated by this group, using animal models and human cells and tissues.

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Michael J. Paidas, MD
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Ms. Guomao Zhao and Drs. Irina Buhimschi and Catalin Buhimschi study proteomic biomarkers in the Perinatal Research Laboratory to understand the causes of preterm birth and preeclampsia.
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Selected Key Publications (of 44 for the academic year):


Meade ES, Ma YY, Guller S. Role of hypoxia-inducible transcription factors 1alpha and 2alpha in the regulation of plasminogen activator inhibitor-1 expression in a human trophoblast cell line. *Placenta.* 2007;28:1012-1019.


Dr. Charles J. Lockwood reviews an experimental protocol with members of his research team.
Preterm birth is currently the largest public health problem facing Ob/Gyn practitioners and its incidence has been rising. The Yale Department of Obstetrics, Gynecology and Reproductive Sciences has made preterm birth one of its top research focuses, and the March of Dimes Foundation has recognized Yale’s prominence in the field. Two of the Foundation’s six annual research grants were awarded for the 2006-2009 period to investigators in the department. One went to department chair Charles Lockwood, MD, and the other to Errol Norwitz, MD, PhD, professor and section co-chief for Maternal-Fetal Medicine.

Lockwood studies the prematurity-enhancing role of thrombin in placental abruption, a condition that often provokes early preterm birth. His team is examining how thrombin, generated by the tissue factor-rich uterine decidua during abruption, interferes with the action of progesterone, a hormone that maintains uterine quiescence and whose suppression is involved in the onset of labor. The team has found strong evidence that thrombin causes effective progesterone withdrawal by down-regulating progesterone receptors in the decidua. Among other mechanisms, thrombin dramatically upregulates the production of the inflammatory cytokine IL-8 to recruit and activate neutrophils to areas of abruption, even when no infection exists. Thrombin also leads to the production of matrix metalloproteases, which attack the extracellular matrix of the decidua and fetal membranes and may lead to premature rupture of the membranes, and IL-6, which increases local prostaglandin production to further promote inflammation and labor.

Circulating thrombin-antithrombin complexes, says Lockwood, are a good predictor of preterm premature rupture of the membranes in asymptomatic women in their second trimester, and may become part of a prenatal screening practice in the future. The results have been presented at March of Dimes symposia in Siena, Italy, and Dallas, Texas, and the Society for Gynecologic Investigation meeting in Glasgow. The department chair next plans to zero in on the molecular mechanisms by which thrombin inhibits progesterone receptor expression. “We might be able to design targeted interventions if we understand better what’s signaling this down-regulation,” he says.

Norwitz studies progesterone action on the uterus. Progesterone is known to be an effective means of preventing preterm delivery when exogenously administered to women who are at risk due to a previous spontaneous preterm birth, but it only works in about one-third of such women. The March of Dimes grant has enabled his team to investigate the genetics of the progesterone receptor, and has funded an ongoing clinical study to characterize in detail the effects of progesterone on the uterus in a group of women who are undergoing planned cesareans. “Progesterone is not a panacea,” says Norwitz. “But if we can understand how progesterone works to prevent recurrent preterm birth in that one-third of women where it is effective, then we may be able to develop new approaches to prevent preterm deliveries in all women.”

Prematurity accounts for the excess of infant mortality observed in the United States, with one in eight babies born before 37 weeks’ gestation in the year 2005—a 15 percent increase from 1995 and an astonishing 36 percent increase from the early 1980s. The etiologies of this increase are many, ranging from older maternal age to the rise of assisted reproductive technologies. Lockwood and Norwitz are among many researchers in the department focusing on preterm birth. “We’re hoping that when people around the country ask themselves who’s doing the best research in preterm birth, they think of Yale,” said Norwitz.
CANCER BIOLOGY GROUP

Cancer cells disrupt normal mechanisms that control cell growth. The Cancer Biology Group studies various aspects of cell signaling that cause or support carcinogenesis and is focused on translating its 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 123I for SPECT imaging of breast cancer, and androgens labeled with 18F for PET imaging of ovarian and prostate cancer. These radio-labeled compounds allow the detection and localization of cancers by hormone receptor mediated uptake. In addition, his laboratory has 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.

Several laboratories are studying oncogenic development transmitted through communication initiated by the epidermal growth factor receptor (EGFR) system. Dr. Jill Reiter’s laboratory studies the functional role of soluble EGFR splice variants in regulating growth factor levels and receptor activity as a mechanism of negative feedback regulation of EGFR signaling. Her lab is also interested in measuring quantitatively the expression of EGFR splice variants in tumor cells. Studies are being conducted to determine whether they might be potential tumor markers in breast, endometrial and ovarian cancers and whether their expression levels might aid in selecting the most appropriate therapy for patients.

Dr. Nita Maihle’s laboratory is interested in whether ligand-dependent and ligand-independent signaling (i.e., cell survival signaling and oncogenic signaling) may be interrelated. In addition, soluble EGFR is being investigated as a potential serum biomarker in breast and ovarian cancer patients for early detection, disease recurrence and monitoring responsiveness to targeted therapeutics during clinical trials.

Dr. Yingqun Huang has been studying the RNA-binding protein Lin28, and has shown that specific repression of Lin28 using siRNA results in decreased cell proliferation and that increased expression of Lin28 accelerates cell proliferation. Consistent with a role in cell cycle regulation, she 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 overexpressed in many cancers of epithelial origin, 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-expressing cells to elicit specific and efficient gene silencing and thereby cancer cell death.

Dr. Gil Mor’s laboratory is interested in the detection and treatment of ovarian cancer and has developed a new test for the early detection of ovarian cancer in high-risk patients. This test utilizes a number of different biomarker proteins whose concentration in blood may be altered in women with ovarian cancer. The test is undergoing further testing to ascertain its sensitivity and specificity with the objective of making it widely available for the detection of this disease in high-risk populations. In addition, his lab has isolated and characterized ovarian cancer stem cells, which may represent...
the source of cancer recurrence. The Mor lab has identified a unique microRNA profile that differentiates these cells from other malignant ovarian cells. One of these, mir-199A, is a major regulator of the NFκB pathway, and could be used as a therapeutic target and a marker for differentiation. In addition, they have 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.

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 the 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 herceptin (Trastuzumab), an anti-HER2neu humanized antibody FDA-approved in breast cancer patients, in patients with chemotherapy-resistant uterine serous papillary carcinoma (i.e., the most biologically aggressive subtype of endometrial cancer). 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. Arimidex (Anastrozole), an aromatase inhibitor approved by the FDA in breast cancer patients, is also under investigation by Dr. Santin’s research group in patients harboring chemotherapy-resistant endometrial carcinoma with encouraging clinical results.
Drs. Santin and Bellone review the results of microarrays used to analyze the global gene expression profile of ovarian carcinoma.
A SURPRISE FINDING SHEDS LIGHT ON OVARIAN CANCER STEM CELLS

An accidental discovery put Yingqun Huang, MD, PhD, assistant professor in our Cancer Biology Group, on the trail of a new therapeutic target for ovarian cancer—and shed light on recently discovered ovarian cancer stem cells.

Intending to study the role of Lin28B—a protein that is overexpressed in hepatocellular carcinoma—in ovarian cancer, Huang decided to screen some cell lines with PCR. Because she happened to have extra RNA primers of the related protein Lin28, she included those among the probes. Many of the cancer cells lit up, but not with Lin28B. They were expressing Lin28. Ordinarily Lin28 is found only in early embryogenesis and adult skeletal and cardiac muscle. It is considered an embryonic stem cell marker, so it was unusual to find it in adult cancer cells. The discovery piqued Huang’s interest in Lin28, and it led her to question just what kinds of cells she was looking at.

“I always thought Lin28B was a ‘bad’ protein—it’s associated with cancers—and Lin28 associated with normal [cells], but it looks like that’s not the case,” she said. “It was quite a surprise.”

Huang then found that some of the ovarian cancer cells expressing Lin28 also expressed Oct4, another stem cell marker. Because neither marker is typically found in differentiated cells, Huang suspects that she may have stumbled upon ovarian cancer stem cells. 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 cancer cells, they are thought to be responsible for tumor initiation, growth, metastasis and relapse, and may represent crucial targets for chemotherapy. Killing the stem cells selectively might not only treat the cancer but also prevent the relapses that often occur after currently available chemotherapies. Finding CSC markers is a crucial step in singling them out.

To further flesh out her findings, Huang is currently studying Lin28 in embryonic stem cells. She is seeking membrane markers that may be co-expressed with Lin28 and Oct4. Finally, she is investigating whether Lin28 is involved in enhanced expression of anti-apoptotic genes. Lin28 is known to inhibit at least one inhibitory protein, Let7, which is down-regulated in lung cancers, and it can also regulate the cell cycle via several other pathways.

If Lin28 is indeed enhancing anti-apoptotic genes, it may make a good therapeutic target. Targeted cells might be rendered more sensitive to chemotherapy—an important consideration in ovarian cancer, which is notoriously chemoresistant, particularly when it recurs. “You knock it out, and then all those [proliferative mechanisms] are gone,” Huang said. “At least you slow down the cells.”
REPRODUCTIVE PHYSIOLOGY GROUP

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.

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Members of the Reproductive Physiology Group review results of experiments designed to test the effects of environmental contaminants on hormone signaling.
Selected Key Publications (of 11 for the academic year):


**DOES ENDOMETRIOSIS ARISE FROM STEM CELLS?**

Experts believe that approximately 15% of reproductive-age women suffer from endometriosis, frequently resulting in pelvic pain and infertility. However, for such a prevalent disease, we have a poor understanding of endometriosis.

Traditionally, researchers believed that endometriosis arose from retrograde menstruation. However, since all women experience retrograde menstruation, this explanation does not address why only some women develop endometriosis. Retrograde menstruation also fails to explain how endometriosis can occur outside the peritoneal cavity.

New findings from our laboratory indicate that endometriosis may have its origins in stem cells, particularly bone marrow-derived mesenchymal stem cells. In 2004, our laboratory first demonstrated that bone marrow-derived mesenchymal cells could be recruited to the endometrium, where they could then differentiate into both endometrial stromal and epithelial cells. We reported in *JAMA* that women who had undergone bone marrow transplants had a substantial number of donor-derived endometrial cells. It became clear that the endometrial cavity could be reconstituted from a stem cell source.

The clinical implications of this finding are profound. The endometrium may be able to remodel or repair itself in response to pregnancy or damage. Additionally, these findings may explain how severe Asherman’s syndrome can be repaired and the endometrium regenerated. The recruitment of new stem cells to the uterus may also explain why endometrial ablation/resection procedures often fail, even when a clinician fully removes the entire endometrium. Further understanding of stem cell recruitment and differentiation will have clinical implications for women suffering from Asherman’s syndrome or abnormal uterine bleeding.
More recently, we reported that bone marrow-derived stem cells could also lead to endometriosis in a mouse model. In the journal Stem Cells in 2007, we demonstrated that, after removing the uterus of the mouse so that endometriosis could not arise from endometrial cells, bone marrow-derived stem cells could still contribute to endometriosis. In this animal model, stem cells populated endometriotic implants, leading to disease progression.

Stem cells appear to play an important role in tissue repair and regeneration. We now understand that stem cells may also lead to disease. Ectopic differentiation of stem cells is a novel mechanism of disease that likely underlies some forms of endometriosis. One of the goals of our research is to better understand how stem cells may contribute to the development of endometriosis, with the ultimate aim of developing preventive or effective treatment strategies.
CHEMICAL WIDELY USED IN PLASTICS ADVERSELY AFFECTS PRIMATE BRAIN

Csaba Leranth, MD, PhD, made headlines worldwide recently with his finding that the common chemical bisphenol-A (BPA) abolishes estradiol-mediated synapse formation in the primate brain, even when administered at a level deemed safe by the U.S. Environmental Protection Agency.

In a study published in *Proceedings of the National Academy of Sciences*, Leranth’s team ovariectomized 12 female monkeys, then gave three a four-week course of estradiol, three BPA, and three both with three vehicle-treated controls. After a month, the controls had a low number of synapses in the hippocampus and prefrontal cortex, while that of estradiol-treated animals was high. In monkeys that received BPA, and in those that received both estradiol and BPA, the number of synapses was as low as in the control group; BPA had completely overcome estradiol’s synapse-building effect. Leranth’s was the first evidence of a direct effect of BPA on the primate brain.

The results are of concern because spine synapse remodeling is thought to be critically important to learning and memory, and 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 am most concerned that the exposure of infants and young children could be harmful,” said Leranth.

BPA is found in many plastics, from baby bottles to the lining of food cans, and humans are constantly exposed as the chemical leaches into food and drink. Though its health effects are controversial, the Canadian government has formally declared it hazardous.

Leranth and his colleagues plan behavioral studies in 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.
MEDICAL STUDENT EDUCATION

Jessica Illuzzi, MD, MS
Ob/Gyn Clerkship Director, Director of Medical Studies

France Galerneau, MD
Ob/Gyn Reproductive Module Director

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 will present to them.

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 curriculum focuses on normal reproductive physiology including embryology, puberty, the menstrual cycle, human sexual response and maternal-fetal physiology. In the second year, 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, 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 for common gynecologic problems. In the hospital, students participate in the intrapartum and postpartum care of women as well as those undergoing gynecologic surgery. In addition, each week we offer a series of well-received didactic, interactive lectures and case-based sessions, including a weekly evidence-based medicine debate 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,

Education

Full-time and community faculty members celebrate their teaching in excellence role.
Gynecologic Oncology, Ambulatory Obstetrics and Gynecology, and an off-site elective at a health services clinic on an American Indian reservation in Gallup, New Mexico.

We host an annual Medical Student and Faculty Ob/Gyn Research Hour to introduce students to the broad range of research topics and opportunities in reproductive sciences. In addition, we organize an ACOG-sponsored Ob/Gyn Student Interest Group to which we invite obstetrician-gynecologists in the community to discuss practice and lifestyle issues. We guide all students expressing interest in applying to Ob/Gyn residencies and provide comprehensive mentoring regarding career development. During the past year, all of our students desiring a residency in Obstetrics and Gynecology matched at their first-choice programs.

We are proud that Dr. Illuzzi’s significant efforts at improving the clerkship program have been recognized by the students who awarded her the Yale Medical School Bohmfalk Teaching Prize in 2007.
STERLING EDUCATION FOR RESIDENTS AND STUDENTS ALIKE

Thursday morning, 11 AM: A medical student argues that mothers should formula-feed their babies. No, she’s not misinformed or behind the times. She and another student have been asked to debate formula-feeding versus breastfeeding. Classmates break in with questions, while residency alumna and clerkship director Jessica Illuzzi, MD, teaches them how to sort through and think about the evidence.

Evidence-based debates, required of both rotating medical students and residents in the Department of Obstetrics, Gynecology and Reproductive Sciences, are only one of the activities that have made the department a national leader in education.

“We have this amazing history of having trained more university chairs than any other department in the US,” says Charles Lockwood, MD, chair of the department and an alumnus of the Department’s Maternal-Fetal Medicine Fellowship Program himself.

What gives Yale that edge? Starting with the best doesn’t hurt. Arriving residents are disproportionately MD/PhDs and have scored an average of 240 on the USMLE. One-third have been elected to Alpha Omega Alpha. “We’re lucky because we get some of the best students,” claims residency director Errol Norwitz, MD, PhD.

Those residents then embark on a hands-on, research-heavy educational journey, supported by dedicated faculty. Didactics are always taught by faculty and are subject to criticism by residents. Journal article reviews are in debate form. A NOELLE robot birthing simulator is used to teach birthing techniques, with more complex simulations planned. Research time is protected, and travels to domestic conferences are paid for by the Department if a resident will present. “Most get a couple of publications under their belt before they finish residency,” Norwitz says.

The faculty’s dedication sets the tone. “A lot of [the faculty] have gone through this program before, and I feel like they see themselves in us,” relates Omar Young, MD, a first-year resident. Mentorship is emphasized, with attendings providing residents with both research and personal support. Private attendings also participate extensively in resident education. One community physician, for example, is developing a training module to teach robotic surgery. “This is a busy private practitioner who gives up his time to help train the residents, which is a testament to the dedication of our community-based faculty,” says Norwitz.

Such training, with its emphasis on active questioning and critical thinking, produces physicians who are “much less docile about accepting the status quo,” Lockwood explains. “We turn what is otherwise a technical apprenticeship…into something much more interesting and stimulating.”

For their part, the residents relish teaching the students. “It’s not only my job, but a privilege to be able to teach them something about Ob/Gyn,” says Young of his daily interactions with medical students. “I want to have them come away with a notion that this [specialty] is really cool.”

The Department has already made one convert this year. “I wasn’t planning on going into Ob/Gyn,” says third-year medical student Laura Cooney during a break in the formula-feeding debate, confessing that she hadn’t even bought the textbook at first. “But this rotation changed my mind.”

Left to right: Resident Adam Gafni-Kane, Program Director Dr. Errol Norwitz, Medical Studies Director Dr. Jessica Illuzzi.
STUDENT TESTIMONIALS
Anonymous student evaluations of the Ob/Gyn Clerkship rotation:

“The clerkship’s most positive experiences were easily the interactions with the fantastic resident staff. Obstetrics especially can be a daunting place where people are constantly running around and have little time for you. However, the residents and interns continually made efforts to get students involved and to make sure they were getting a rewarding experience. They taught, listened, chatted and near juggled bowling pins in order to make sure the students got the experiences the residents wanted when they were students. So major kudos to the Department for selecting such great teachers and people in general.”

“I think the MFM sub-I was a wonderful experience … [and] all of the residents, fellows and attendings were absolutely great. They were all knowledgeable and willing to teach. The strengths of the rotation are the level of responsibility you are given, the opportunity to attempt a procedure and to be involved in patient care, and the variety of experiences you have.”

“My Ambulatory Ob/Gyn sub-internship provided excellent exposure to being an Ob/Gyn! I was exposed to a varied patient population with many Ob/Gyn issues, which provided an opportunity to learn more about everything from prenatal care to adolescent health to post-menopausal health to gynecologic oncology, quality-of-life and end-of-life issues. I spent time with patients and their families discussing their illness or pregnancy and the effect they have on their routine life. I loved the opportunity for primary care, health maintenance and anticipatory guidance. The sub-I provided excellent exposure to different attending styles, a chance to practice working with many different people in different clinical settings and to act autonomously under supervision. I also valued the opportunity to investigate the evidence for the plans of care executed day to day in the prenatal, urogyn and gynonc clinic. I would encourage any student to consider this rotation during their fourth year even if only remotely thinking about Ob/Gyn. This might win them over!”
RESIDENCY PROGRAM

Errol R. Norwitz, MD, PhD
Program Director

Julia Shaw, MD, MBA
Associate Program Director

Stephen Thung, MD
Assistant Program Director

Christian Pettker, MD
Assistant Program Director

Anna Sfakianaki, MD
Assistant Program Director

Marsha Guess, MD
Assistant Program Director

France Galerneau, MD
Assistant Program Director

Mission Statement
The primary goal of the Obstetrics and 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 six categorical resident positions per year. The program remains extremely competitive, and the number of applications as well as the strength of the applicants has been increasing year by year. During the 2008 residency recruitment season, we received over 400 applications, 363 from U.S. medical schools, and interviewed approximately 80 candidates, all of whom had a track record for academic excellence, public service and a passion for women’s health care. We continue to attract and recruit some of the top students from medical schools around the country.

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 lead the Gynecology and Obstetrics Morning Report each day. Faculty

Residents and students use the laparoscopic simulator, one of many simulation tools, in order to learn and master surgical skills needed in the O.R.
review patient cases and assist the resident staff in devising clear and rational plans of management, using the principles of evidence-based medicine. A state-of-the-art interactive computer system allows the team to review radiologic imaging studies, laboratory data and fetal heart rate tracings in real time during Morning Report.

Thursday afternoons are reserved for didactics, 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. One hour per week is also set aside for CREOG reviews, Journal Club, professionalism seminars, and micro-seminars to familiarize the residents with issues relating to medical malpractice insurance, litigation, risk management and effective patient communication.

**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, and residents are encouraged to take advantage of these opportunities. 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 in time to present them at our annual Residents’ Research Day. These initiatives have been enormously successful, and a number of residents were invited to present their research at national and international Ob/Gyn scientific meetings. A number of residents also had their research accepted for publication in highly respected peer-reviewed journals.

**Accomplishments 2007-2008**

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

1. We introduced a comprehensive two-week PGY-1 orientation at the beginning of the intern year, which includes hands-on training in basic obstetric and gynecologic ultrasound and electronic fetal monitoring.
2. Organized a cadaver laboratory 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. Introduction of a hands-on laparoscopic simulator model and a “virtual reality” computer-simulated trainer (LapSim®), both designed to teach laparoscopic surgical technique.
5. Introduction of obstetric simulation drills using the NOELLE birthing simulator to improve management decisions and communication skills.

**Proportion of Chief Residents Who Match Into Fellowship Training Programs**

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<th>PGY-4 academic year</th>
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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 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.

Selected Publications with Residents as Authors:


