

Winter 2008



Advancing Ob/Gyn

Developments from Yale Obstetrics,
Gynecology & Reproductive Sciences

Message from the Chair

**Greetings from Charles J. Lockwood, MD, The Anita O'Keefe
Young Professor of Women's Health and Chair**

I am most pleased to introduce you to the Winter 2008 issue of *Advancing Ob/Gyn*. As has become our tradition, inside you will find reports of recent clinical developments and research in progress at Yale Obstetrics, Gynecology & Reproductive Sciences. While we have many significant advances in our three mission areas of education, clinical care, and research, we have selected only those topics that we believe will be most relevant to you as medical professionals.

In this issue, we chose to highlight clinical developments that cross the traditional subspecialty boundaries, as is the case for fertility preservation in women with cancer and robotic-assisted laparoscopic gynecologic surgery. As in past issues, we expect that the information you will find here will have a positive impact on your practice.

We hope that the topics covered in our newsletter will serve as a valuable source of contemporary thinking for ob/gyns, internists, midwives, fellows, and residents. As always, we welcome your comments and suggestions.

Charles J. Lockwood, MD

Yale Obstetrics and Gynecology
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Fertility Preservation Options for Women Undergoing Chemo- or Radiotherapy

Jason G. Bromer, MD and Emre Seli, MD



Cancer is not as rare among younger women as one might expect; approximately 600,000 US women are diagnosed with cancer every year, and 10% of them are under 40 years old. The treatment required may involve either removal of the ovaries or cytotoxic treatment that impairs reproductive function. Because cancer survival has improved in recent years, there is an increased focus on quality-of-life issues for female cancer survivors, including those related to fertility.

Currently, the only widely available option for fertility preservation in female patients who need chemo- and/or radiotherapy is cryopreservation of embryos, which involves exposure to cryoprotectants, cooling to subzero temperatures, and storage.

The embryos then may be thawed on demand and transferred to the uterus.

Despite well-defined success rates, embryo cryopreservation has some critical shortcomings. First, the patient must have a male partner or use donor sperm to fertilize retrieved eggs. Second, it necessitates a delay in the initiation of chemo- or radiotherapy that may not be acceptable. Third, the high serum estrogen concentrations associated with ovarian stimulation may be contraindicated in women with estrogen-sensitive malignancies such as breast cancer.

An alternative approach is the cryopreservation of unfertilized oocytes; while still experimental, this technique has become increasingly

common. Although still requiring ovarian stimulation, oocyte cryopreservation avoids the need for sperm and thus is available to a larger group of patients than is embryo cryopreservation.

Success rates using frozen oocytes have traditionally lagged

behind those using frozen embryos. However, newer techniques including slow freezing, vitrification, and improvements in cryoprotectants have begun to yield more favorable pregnancy rates.

Another approach to preserving fertility is cryopreservation of primordial follicles within ovarian tissue without the necessity for ovarian stimulation and delay in initiating cancer treatment. Primordial follicles are less susceptible to cryo-injury due to their smaller size, slower metabolic rates,



Ovarian cortical tissue prepared for cryopreservation.

and the absence of a zona pellucida. Although experimental, two approaches to ovarian tissue cryopreservation are currently under investigation: cryopreservation of ovarian cortical strips and cryopreservation of whole ovaries.

All these options are available at Yale Fertility Center, where experimental procedures are offered under research protocols approved by our institutional review board.

For a more detailed discussion of this topic, as well as author bios, please visit www.yaleobgyn.org/advancing.

Characteristics	Oocyte cryo	Ovarian tissue cryo
Requires ovarian stimulation	Yes	No
Requires delay in chemotherapy	Yes	No
Requires surgery	No	Yes
Risk of reseeded cancer	No	Yes
Appropriate in prepuberty	No	Yes
Resumption of endocrine function	No	Yes
Human live birth	Yes	2 cases

[Bianchi V, Johnson J, Seli E, 2008]

Oocyte and ovarian tissue cryopreservation: differences and indications.

Robotic Gynecologic Surgery at Yale Ob/Gyn

Masoud Azodi, MD

Laparoscopic surgery has benefited greatly from the technological advances of the last two decades. In 2005, the FDA approved the use of the *da Vinci*[®] Surgical System for gynecologic indications and pelvic surgeons rapidly adopted the technology. Robotic laparoscopic surgery offers great advantages to our patients as well as to our physicians. Surgeons can now operate in an ergonomic position and with improved hand-eye coordination.

Robotic-assisted laparoscopy overcomes many of the limitations of conventional laparoscopy. The greatest benefit accrues with obese and morbidly obese patients. Robotic technology facilitates the performance of pelvic surgery in these patients without complications and with short hospitalizations. Even patients with malignant obesity or super morbid obesity have been discharged from the hospital on postoperative day one and have had an uneventful postoperative course.

The studies published using the *da Vinci*[®] Surgical System in gynecology document the feasibility and safety of this approach in pelvic surgery. The evolving literature on robotic-assisted surgical procedures demonstrates that the limitations of conventional laparoscopy can be overcome by the adoption of robotic technology, enhancing the surgeon's laparoscopic skills.

Yale Gynecologic Oncology Program faculty have performed nearly 300 surgeries using this technology, including 13 radical hysterectomies for treatment of cervical cancer. With robotic-assisted laparoscopy, we are able to offer minimally invasive surgery to morbidly and super morbidly obese



patients with excellent outcomes and shorter hospital stays. We have also successfully used this technology to treat difficult benign cases including large uterine fibroids and vaginal wall suspension for pelvic floor dysfunction.

Similarly, physicians at Yale Reproductive Endocrinology are using the *da Vinci*[®] Surgical System to facilitate difficult reproductive endocrinology laparoscopic procedures such as the treatment of advanced endometriosis, which will likely improve surgical outcomes in these cases.

For a more detailed discussion of this topic, as well as an author bio, please visit www.yaleobgyn.org/advancing.

da Vinci images ©[2008] Intuitive Surgical, Inc.





A New Method for Embryo Selection: Metabolomics

Emre Seli, MD

Infertility centers in the United States attain high success rates following *in vitro* fertilization (IVF), often through simultaneous transfer of multiple embryos. In 2006, IVF programs transferred a mean number of 2.45 embryos during IVF cycles, leading to a 34.3% live birth rate, of which 32.0% were multiple-infant live births. Even in cases where embryos possessed the highest reproductive potential (oocyte donation), programs transferred a mean number of 2.3 embryos and 40.8% of the pregnancies resulted in multiple-infant live births. In total, more than 30% of ART pregnancies are twins or higher-order multiple gestations. Consequently, decreasing

multiple gestations while maintaining or improving overall pregnancy rates remains a significant goal in today's infertility treatment.

The sentinel issue surrounding multiple gestations following IVF is the inability to estimate the reproductive potential of individual embryos. Current grading systems are not sufficiently precise to compel most patients and clinicians to reduce the number of embryos transferred to a point where twins are uncommon and higher-order multiple gestations are rare or eliminated.

Such limitations have led many investigators to pursue adjunctive technologies for assessment of an

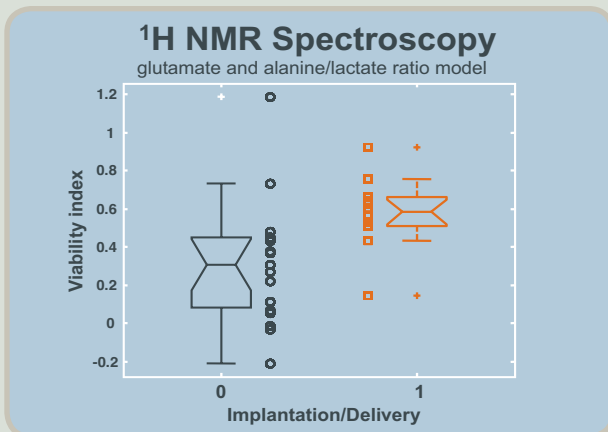
embryo's reproductive potential. However, these technologies are expensive, require costly dedicated equipment and technical staff, and frequently do not produce results quickly enough to be used within the acceptable window of time for embryo transfer. Because none of the technologies have been validated, the

need remains to identify a method that predicts embryo viability through a rapid, non-invasive, consistent, and clinically applicable platform.

Drs. Emre Seli and Denny Sakkas from our Department, in collaboration with Prof. Dave Burns from McGill University and Molecular Biometrics, Inc., recently reported results from a multi-center study using a non-invasive spectroscopic method for prediction of the implantation potential of embryos in IVF. Spectroscopic analysis and bioinformatics, also called metabolomics, successfully predicted the implantation potential of embryos. They confirmed these results in a second trial and predicted outcome with a sensitivity of more than 70%.

The research team has recently presented the results of this study at the American Society for Reproductive Medicine (ASRM) annual meeting, where the work was selected as a prize paper candidate. This technology is expected to be available worldwide before the end of the academic year.

For a more detailed discussion of this topic, as well as an author bio, please visit www.yaleobgyn.org/advancing.



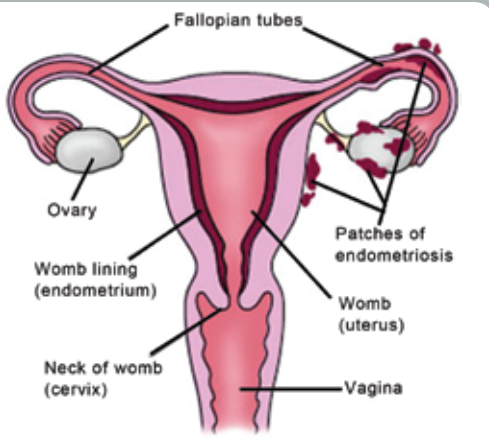
Spectroscopic analysis of culture media differentiates between embryos that implant and result in delivery from those that fail to implant.

Does Endometriosis Arise from Stem Cells?

Hugh Taylor, MD

Traditionally, researchers believed that endometriosis arose from retrograde menstruation. However, since all women experience retrograde menstruation, this explanation does not address why only some of them develop endometriosis.

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.



Typical sites of endometriosis in the pelvis.

Traditionally, researchers developed the theory that endometriosis arises 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 demonstrated that bone marrow-derived stem cells

could also lead to endometriosis in a mouse model. In the journal *Stem Cells* in 2007, we reported 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.

For a more detailed discussion of this topic, as well as an author bio, please visit www.yaleobgyn.org/advancing.

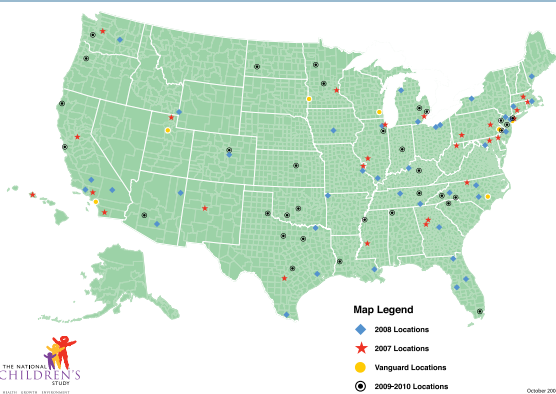


National Children's Study: Largest Study on How Genes and Environment Affect Children's Health

Jessica Illuzzi, MD

The Yale Center for Perinatal, Pediatric, and Environmental Epidemiology has received a \$10.7 million grant to expand its participation in the National Children's Study, which will recruit 100,000 pregnant women throughout the country and follow their children until age 21. Last year the Center received a \$15 million grant and began work in New Haven County; the new grant will extend the study's scope to include Litchfield County in northwestern Connecticut.

National Children's Study Locations



Yale is one of the academic medical centers selected to recruit a sample of women from all over the US into the National Children's Study.

counties in the US, with 13 to 15 neighborhoods in each county, to represent the diversity of the US population. The study will explore the effects of environmental factors on the health and development of children. Outcomes studied will include asthma, obesity, and autism, as well as less common outcomes, such as childhood cancers.

The National Children's Study represents a once-in-a-lifetime opportunity to study early precursors of disease. Members may propose adjunct studies to the National Coordinating Center at the NICHD; contact Dr. Illuzzi if you have suggestions for such studies.

For a more detailed discussion of this topic, as well as an author bio, please visit www.yaleobgyn.org/advancing.

Drs. Jessica Illuzzi and Heather Lipkind from our Department are Ob/Gyn investigators on both grants. Dr. Illuzzi serves as the study director for the New Haven County grant while Dr. Lipkind is the Maternal-Fetal Medicine consultant for both the New Haven and Litchfield sites.

The National Children's Study is the largest of its kind in the US. Researchers selected a statistical sample of 105



Seven Yale Ob/Gyn Physicians Included in *New York Magazine's* Top Docs List

New York Magazine's 11th annual "Best Doctors" issue, which highlights the top doctors in the New York metropolitan area as determined in a peer-review survey conducted by Castle Connolly Medical Ltd., included seven physicians from Yale's Department of Obstetrics, Gynecology & Reproductive Sciences. The complete listing of 6,000 doctors represents the top 10 percent of the region's physicians as nominated by their fellow medical professionals. Nomination is based on a number of criteria encompassing professional qualifications, reputation, and patient skills.

We congratulate the following faculty members, two of whom completed residency training and five of whom graduated from their clinical fellowships at Yale, for their inclusion in this prestigious listing:

Gynecologic Oncology:

Thomas Rutherford, PhD, MD*
Peter Schwartz, MD**

Maternal-Fetal Medicine:

Joshua Copel, MD* **
Charles Lockwood, MD*
Michael Pidas, MD

Reproductive Endocrinology and Infertility:

Pasquale Patrizio, MD***
Hugh Taylor, MD* **

* Clinical Fellowship at Yale

** Residency: Yale Ob/Gyn

*** Also named in *Women's Health Magazine's* "Top Doctors for Women" list

Featured Physician: Kathleen Connell

Kathleen Connell, MD, is an Assistant Professor in the Department of Obstetrics, Gynecology & Reproductive Sciences and a physician at Yale Urogynecology and Reconstructive Pelvic Surgery. She is ABOG-certified and fellowship trained in Female Pelvic Medicine and Reconstructive Surgery. Dr. Connell specializes in abdominal, vaginal and laparoscopic surgical approaches to treat uterine and vaginal prolapse, as well as urinary and fecal incontinence.

Dr. Connell's seminal work, which identified a genetic pathway involved in the development of pelvic organ prolapse, was recently published in the *Journal of Clinical Investigation*. Currently, Dr. Connell is one of three Yale Women's Reproductive Health Research Program Scholars sponsored by the National Institutes of Health.



Developmental Genes and the Pelvic Support System: Understanding the Genetic Basis of Pelvic Organ Prolapse

Kathleen Connell, MD

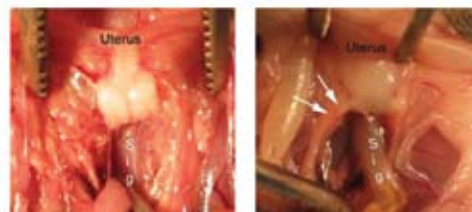
Pelvic organ prolapse (POP) is a common, costly, and debilitating disorder that negatively impacts quality of life for many women. During POP, a woman's pelvic organs descend, causing symptoms that include urinary and fecal incontinence, pelvic pain, and sexual dysfunction.

POP is one of the most common diagnoses leading to hysterectomy; however, the recurrence rate after surgical intervention for POP is very high. While scientists have a poor understanding of the molecular mechanisms responsible for maintaining pelvic organ support structures, one proposal hypothesizes that alterations in remodeling of the pelvic floor after childbirth trauma, compounded by age, parity, menopause and BMI, lead to gradual weakening of the pelvic support system.

The paired uterosacral ligaments (USLs), consisting of smooth muscle and collagen, are key structures in this



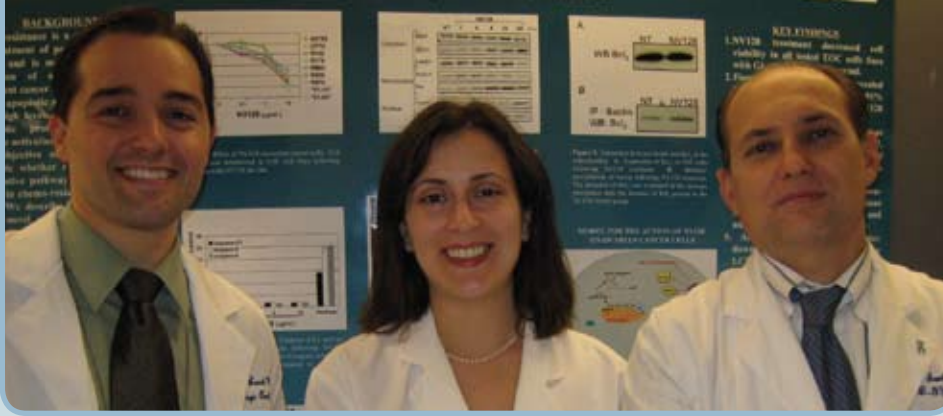
system. My colleagues and I have shown that in mice a developmental homeobox (*HOX*) gene, *HOXA11*, may be an important regulator of the integrity of the USLs and that the protein encoded by *HOXA11* is an essential molecular factor for the development of USLs. This led us to suggest that changes in *HOXA11*-regulated pathways might weaken USLs and thereby cause POP.



Comparison of *HOXA11* null (left) with wild type (right) mouse pelvic anatomy shows congenital absence of USL in the *HOXA11* null mouse.

The identification of molecular pathways and genetic markers for POP will enable classification of risk for developing the disease. Stratifying women into defined risk categories will help physicians better counsel patients in prevention strategies and risk of recurrence after surgical repair, and possibly reverse the course of disease. Such strategies could include dietary interventions, lifestyle changes, and drug treatments that could potentially avoid repetitive surgeries by reducing the recurrence rate of POP, affording a better quality of life for patients and a reduced financial burden.

For a more detailed discussion of this topic, as well as a full author bio, please visit www.yaleobgyn.org/advancing.



Newest Additions to Our Faculty: Silasi/Kodaman/Santin

Dr. Alessandro D. Santin

Alessandro D. Santin, MD, a native of Italy, trained at the University of Brescia, Italy, was on the faculty of the University of Arkansas for Medical Sciences, and joined our faculty in the Section of Gynecologic Oncology as Professor in July 2008.

Among his honors, he received the American Association of Cancer Research's Young Investigator Award and the Italian Society of Gynecologic Oncologists Award for Translational Science.

Dr. Santin's clinical interests include cancer of the ovary, uterus, vagina, cervix and vulva; intraperitoneal chemotherapy, tumor immunology and immunotherapy; and tumor angiogenesis, radiation biology, and experimental therapeutics in gynecologic oncology.

For more detailed physician bios, please visit www.yaleobgyn.org/advancing.

Dr. Dan-Arin Silasi

Dan-Arin Silasi, MD, joined the Section of Gynecologic Oncology as Assistant Professor in July 2008. He began his medical training in Romania, with residencies at NYU and the University of Texas, arriving at Yale as a fellow in Gynecologic Oncology in 2005. While a fellow, he received the José Asis Memorial Award for excellence in teaching residents.

Dr. Silasi has distinguished himself as a gynecologic surgeon, a teacher, and a translational researcher. His clinical interests include contemporary therapeutic options for gynecologic malignancies, with a special interest in robotic surgery.

Dr. Pinar Kodaman

Pinar Kodaman, MD, PhD, joined the Section of Reproductive Endocrinology and Infertility in the Department of Obstetrics, Gynecology & Reproductive Sciences as Assistant Professor in July 2008. She attended Yale Medical School in the combined MD/PhD program, researching the role of oxidative stress in ovarian function.

Following graduation, Dr. Kodaman joined our fellowship in Reproductive Endocrinology and Infertility where she is currently a Women's Reproductive Health Research Scholar. Her research interests include endometrial angiogenesis and endothelial dysfunction while her clinical interests include PCOS, reproductive surgery and infertility.

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