YALE OBSTETRICAL AND GYNECOLOGICAL SOCIETY

YOGBS

Spring 2011
Volume 4

THE JOURNAL FOR ALUMNI AND FRIENDS OF YALE OB/GYN
Contributors

Editor-In-Chief – Mary Jane Minkin, MD
Managing Editor – Dianna Malvey

The YOGS Journal is published yearly by the Yale University Department of Obstetrics, Gynecology and Reproductive Sciences, PO Box 208063, FMB 337, New Haven, Connecticut 06520-8063.

Tel: 203-737-4593; Fax: 203-737-1883
On the Web: http://medicine.yale.edu/obgyn/yogs/index.aspx

Copyright © 2011 Yale University School of Medicine. All Rights Reserved.

Cover Photo:
Nathan Smith, First Professor of Surgery & Obstetrics at Yale Medical School.
From the portrait in the Rotunda of Yale Medical School.
Rights: Yale University, Carl Kaufman & William Sacco, Yale Photo & Design.
Copyright 2011 Yale University School of Medicine. All Rights Reserved.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor’s Note</td>
<td>2</td>
</tr>
<tr>
<td>Historical Note</td>
<td>5</td>
</tr>
<tr>
<td>Residents’ Research Day Visiting Professor Grand Rounds</td>
<td>17</td>
</tr>
<tr>
<td>Other Selected Grand Rounds Presentations</td>
<td>20</td>
</tr>
<tr>
<td>Residents’ Research Day - Abstracts of Resident Presentations</td>
<td>42</td>
</tr>
<tr>
<td>Abstracts from Recent Scientific Meetings</td>
<td>50</td>
</tr>
<tr>
<td>The Year in Review</td>
<td>59</td>
</tr>
<tr>
<td>Photo Highlights</td>
<td>66</td>
</tr>
<tr>
<td>News Items</td>
<td>70</td>
</tr>
<tr>
<td>Forms</td>
<td>79</td>
</tr>
</tbody>
</table>
Welcome to our 2011 edition of the YOGS Journal. Although the classical Luddite, I do realize that modernization of the publishing world has occurred, which allows for more information sharing with lower costs. Last year, we were able to share with you some exciting Gyn Oncology videos of robotic surgery on the web. This year, we are going to bring you the full texts of two excellent historical talks by Dr. Kohorn and Dr. Gross. After all, we are celebrating the 200th anniversary of the medical school and our department as well!

Dr. Kohorn's history of the department is printed in full in our electronic version.

Former resident Dr. Gary Gross has written a wonderfully thorough article on Griswold v. Connecticut, the Supreme Court decision that provided, as Dr. Gross describes it, “women the freedom to control their reproductive futures and to achieve entry to education, professions, careers and self-realization beyond that promised by ‘biology is destiny.’”

Dr. Gross’s article is also printed in full in our electronic version; to bring you some of the highlights of what you will find there, here is a bit of a preview:

Griswold v. Connecticut overturned the Comstock Laws, the 1870s legislation which barred dissemination of information about reproduction and birth control even to married couples. Connecticut’s version of these statutes was crafted by P.T. Barnum! In New York, Margaret Sanger raised the first major challenge to the Comstock Laws in 1914, opening her first birth control clinic in Brooklyn in 1916. The Connecticut Birth Control League (CBCL), founded by actress Katharine Hepburn’s mother and her friends, started lobbying the legislature in Connecticut in 1923 to repeal P.T. Barnum’s laws. Dr. Gross outlines all the legislative adventures that occurred in the years through 1961 when the CBCL was renamed Planned Parenthood of Connecticut and they hired Estelle Griswold as their Executive Director. She worked closely with our then chairman, Dr. C. Lee Buxton, and Dr. Virginia Stuermer, who also saw patients at Planned Parenthood. They were arrested for distributing condoms to married couples, and the case ultimately reached the U.S. Supreme Court.

Dr. Gross then describes and analyzes the legal issues surrounding the medical highpoints from 1961 through 1965, including Dr. Buxton’s assertion, when let out on $100 bond, “I thought I was worth more than $100.” As Dr. Gross concludes, “Those of us who have never lived through a world where contraception was deemed illegal can scarcely envision a world where the right to privacy in all its permutations is not taken for granted. We must be wary. Recent events do not portend all that well.” This important article gives us a thorough history of a remarkable time in our department, state and nation. Remember, as George Santayana said, “Those who cannot remember the past are condemned to repeat it.”

Of course, we also want to share with you news of exciting additions to our department and of our latest accomplishments.

In trying to keep everyone up on the latest developments locally and in our specialty, we have selected five Grand Rounds from the past year to share with you. Dr. Haywood Brown came from Duke to educate and entertain our residents on Research Day in June, and he shared a comprehensive view of preconception evaluations at the attendant Grand Rounds. Our chair, Dr. Charles Lockwood, reviewed the current state of inves-
tigation for recurrent pregnancy loss. Dr. Lubna Pal, one of our former residents and now director of our Polycystic Ovarian Syndrome Clinic, updated us on the current state of the art in PCOS. Dr. Gil Mor, whom I always advertise as the only person on earth who can make apoptosis fun and understandable, educated us on his research on ovarian stem cells. Dr. Elizabeth Erekson shared her passion for prolapse work with a review of mesh interventions in surgical approaches to vaginal vault suspensions.

We are also hoping that many of you will be in attendance at our annual YOGS reunion in New Haven on April 2, honoring Dr. Peter Schwartz. In addition to our afternoon scientific talks and our dinner at the Peabody with open mike, we will have an after-dinner (non-scientific!) speaker, Dr. Alan DeCherney. We are looking forward to seeing everyone there.

And of course, you know that I’ll make my usual appeal: If you’re not a YOGS member already, why not? If you’re reading this, you are a member of the family – and it’s a pretty respectable one at that! So send in your dues, and support your alumni association.

Mary Jane
1914...

Left to Right: Dr. Paul Rekers, Dr. Gervase Connors, Dr. Spiers, Dr. Orvan Hess, Dr. John Homans, Dr. Arthur Morse, Dr. Herbert Thoms, Dr. Irving Friedman

2010...
HISTORICAL NOTE

Ernest I. Kohorn, Professor Emeritus, Section of Gynecologic Oncology and Uro-gynecology, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

Ernest I. Kohorn, MA (Cantab), MA (Yale), MChir (Cantab), FRCS (England), FRCOG, FACOG

A History of the Department of Gynecology and Obstetrics at the 200th Anniversary of Yale Medical School

Presented at Grand Rounds, Department of Gynecology & Obstetrics, January 2011. The portion of this history from 1800 to 1965 has been reproduced with permission of the Yale Journal of Biology and Medicine (copyright 1993). It has been abridged and revised. The text since that time is original.

We are currently celebrating the 200th anniversary of the Yale School of Medicine’s Department of Obstetrics, Gynecology and Reproductive Sciences. In 1993, I described the Department’s first 150 years, “from Nathan Smith to Lee Buxton” (1). Today I will recapitulate those 150 years (2) but then will concentrate on the Department’s last 50 years, try to place these recent times into some perspective, and discuss their significance in relation to the present state of medical practice and specifically to obstetrics and gynecology. Many current and distinguished members and graduates of this program may not be mentioned in this account. That needs to await a detailed and more comprehensive future history.

The Yale School of Medicine was the brainchild of President Ezra Stiles (Figure 1), the seventh president of the University and a noted educator, author, Congregationalist minister and theologian. He felt that Yale College should expand to have both a law school and a medical school (2). The founding of the Connecticut Medical Society in 1792 appears to have been a prerequisite for the establishment of the medical school (3). This Society was given the authority to appoint examining committees, to issue medical licenses to those found qualified, and to confer honorary degrees in medicine. It took another 30 years for the Yale Medical School to begin its activities, in part due to the fact that the Medical Society only met formally once a year.

Ezra Stiles died in 1795 and was succeeded by another noted Congregationalist minister, Timothy Dwight (Figure 2), who incidentally was the grandson of the Rev. Jonathan Edwards, one of the greatest early American theologians and famous fiery preacher (1703-1758).

Mason Fitch Cogswell (Figure 3) and Eli Ives (Figure 4), both members of the Connecticut Medical Society, were instrumental in supporting the founding of the medical school at Yale. In 1802 a professorship of chemistry was instituted in Yale College, and Benjamin Silliman (Figure 5) was appointed. He was then studying law at Yale. To prepare himself for this task, Silliman went to Philadelphia, then the center of scientific and medical learning in North America, to study with noted physicians Caspar Wistar, Benjamin Smith Barton and James Woodhouse at the University of Pennsylvania. The first appointment to the
clinical faculty was Mason Cogswell, who was appointed professor of surgery and anatomy, followed by Jonathan Knight (Figure 6) who was appointed assistant professor. Knight was president of the National Medical Convention that in 1846 evolved into the American Medical Association (AMA). Knight also served as president of the AMA from 1853 to 1854.

Cogswell was the leading surgeon in Connecticut and was prominent in civic affairs. He established the first institution in the United States for the treatment of the “deaf and dumb” (his daughter was hearing impaired) and was also the founder of the Hartford Retreat for the Insane. However, Cogswell preferred to stay in Hartford. Eneas Munson (Figure 7), also from Hartford and a founder of the Connecticut Medical Society, was appointed professor of Materia Medica and botany. However, he felt that at age 75, he was too old to lecture to students and, although he maintained his professorship, the actual teaching was performed by Eli Ives, who also became the first lecturer and then professor of Materia Medica. Ives also studied at the University of Pennsylvania under the great Benjamin Rush, Caspar Wistar and Benjamin Smith Barton.

Because Cogswell and Munson did not take up their designated duties, appointing an active teacher and clinician at the new medical school became a matter of urgency. The Yale Corporation finally and successfully invited Nathan Smith (Figure 8) to be the first professor of surgery and obstetrics. We need to note that the portraits of all these individuals are prominently displayed on the upper floor of the rotunda of the Yale Medical School Library right outside the Beaumont Room. Before he came to Yale, Smith had founded three other medical schools, those at Dartmouth College, Bowdoin College and the University of Vermont. At that time, Smith was spending most of his time at Dartmouth where he lectured on anatomy, surgery, chemistry and the theory and practice of physic. Oliver Wendell Holmes later commented that Smith occupied not one chair but a settee of professorships. His income derived from student fees, as each student paid $133 for the required courses, and from his private practice. President Wheelock of Dartmouth, coming from one of Nathan Smith’s lectures, was so inspired that he led the evening prayers: “Oh Lord, we thank Thee for the oxygen gas. We thank Thee for the hydrogen gas and all the gases. We thank Thee for the cerebrum and the cerebellum and the medulla oblongata.” Smith traveled widely across New Hampshire and Vermont, always on horseback and usually with his apprentices. Clinical teaching and discussion went on throughout their journey.

Smith’s appointment at Yale College was initially opposed by President Timothy Dwight, who thought he might be an infidel, a free thinker in the pattern of Voltaire and Rousseau, and to have been influenced by the writings of Tom Paine. After long correspondence between Cogswell and Silliman and Nathan Smith, the Yale College authorities were finally reassured about Smith’s religious orthodoxy, and his appointment as the first professor of the theory and practice of physic,
surgery and obstetrics was confirmed. His was the sixth such appointment in North America.

Smith had a wide repertoire of achievement. He was the second person to operate for an ovarian tumor – July 5, 1821. He did not know of Ephraim McDowell’s feat in Danville, Kentucky, eight years earlier. Smith had performed an autopsy on a patient with this diagnosis previously and confirmed that the pedicle could be ligated without difficulty. Unlike McDowell, he allowed the ligated pedicle to fall back into the abdomen. He realized that typhoid fever was associated with dehydration and recommended fluids and support rather than purging. He treated osteomyelitis conservatively and not by amputation as was the recommended practice at the time. Joseph Smith, who later founded the Mormon religion, developed typhoid osteomyelitis of the tibia at the age of 18. Nathan Smith treated the lad conservatively by draining the pus and removing dead bone fragments, thus avoiding amputation. It is doubtful that an amputee could have gone “West.”

While at Yale, Smith continued his teaching and practice activities at Dartmouth and also Vermont where his second son, Ryno Smith, was professor of anatomy and physiology. Ryno Smith later moved to Philadelphia and helped found Jefferson Medical College. David Paige Smith was appointed to the Ives Chair of the Theory and Practice of Medicine at Yale in 1873. All of Nathan Smith’s four sons, nine grandsons and six great-grandsons entered medicine. Smith died quite suddenly of a “febrile illness” on January 26, 1829, aged 66. Those of you who wish for more detail may consult the article in the Yale Journal of Biology and Medicine from 1993 (1).

The time from then to the beginning of the 20th century is known as a “silent century.” Little academic record has survived. Thomas Hubbard (Figure 9) succeeded Smith to the chair of obstetrics. He was a successful and conscientious surgeon from Pomfret, Connecticut, and remained in the professorship until 1838. Timothy Phelps Beers was the next professor. Beers had received his MD degree from Yale and, although he had a large practice of some 5000 patients, he was a painfully diffident teacher. His lectures in obstetrics, it was said, were illustrative of a “difficult and protracted delivery.”

From the beginning, Yale medical students were required to write a thesis for the MD degree. In 1836 the subject of one of these was “auscultation in pregnancy,” 17 years after Laennec had described the stethoscope; clearly this was the beginning of fetal monitoring.

Pliny Adams Jewett (Figure 10) succeeded Beers. He, however, was appointed surgeon in chief to the Knights Hospital in New Haven during the Civil War. Because of this he resigned his professorship and was succeeded by Thomas Hubbard in 1864. In 1830, Jonathan Knight had suggested to the Yale Corporation that obstetrics and diseases of children merited a separate professorship. Only in 1867 was the professorship changed from “Obstetrics” to “Obstetrics and Diseases of Women and Children.”
However, Hubbard attended only 32 deliveries in 15 years. He was a “difficult and peppery individual.” His appointment marked the first serious controversy in the history of the medical school during its first half-century. In protest, Jonathan Knight resigned his professorship. Finally Hubbard was forced to resign. His successor, Frank Beckwith, had to resign in 1885 because he could not “afford his professorship on the salary he was paid.” The professorial salary was so small that he had to use the wards of the hospital as his private clinic.

In 1871 the New Haven Dispensary had opened on Crown Street and moved to York Street in 1878. A training school for nurses, the second in the United States, opened in 1873 and was housed in what was to become known as the Hope Building. At this time the medical school severed its association with the Connecticut Medical Society and became incorporated as a graduate school of Yale University. The Medical Society provided medical licensure and the University the academic degree of MD. The hospital moved to Congress Avenue in 1873. During the last decade of the 19th century and the first decade of the 20th, the obstetric wards were not used for teaching because the “clinical material” was insufficient, so most senior students took additional courses at New York Lying-In Hospital (now New York Hospital).

Yale was one of the medical schools rated by the 1910 Flexner Report as being “worthy of continuation.” The Department of Obstetrics was the first clinical department at Yale where faculty members were hired on a full-time basis. In 1914, Josiah Morris Slemons, a Hopkins graduate and formerly professor of obstetrics and gynecology at the University of California, was charged with the organization of the formal department. The assistant professor was Arthur H. Morse, also a Hopkins graduate. Herbert Thoms was laboratory assistant. Six years later Slemons resigned to return to his practice in Los Angeles, and Morse (Figure 11) was appointed to the chair that he held until 1945.

Morse was a charter member of the American Board of Obstetrics and Gynecology. It was Morse who invited Gertrude Van Wagenen (Figure 12) to come to Yale to initiate the macaque monkey colony that eventually led to the definitive description of the reproductive physiology of both the female and male macaque. That work also allowed the subsequent discovery of the “morning-after pill.” During his 28 years as chair, there were only 15 publications, all in obstetrics. However, Morse was an “unsparing and fine teacher with insight and deep interest and unfailing kindness… He was always impeccably dressed in a white coat with a fresh flower in his buttonhole.”

The next chairman was Herbert Thoms (Figure 13). He was born in Waterbury, Connecticut, in 1885 and came to Yale Medical School directly from high school. He interned at Backus Hospital in Norwich and Memorial Hospital in New London and did residency training at Sloane Hospital for Women in New York, the first gynecological hospital in the United States, founded by Marion Sims in 1854. Thoms then went to Johns Hop-
kins and joined the Yale faculty in 1915. His major scientific contribution was the introduction and refinements of x-ray pelvimetry. Thom’s view of the pelvis set the standards of the time. It was not until 1967 that the practice of performing full pelvimetry on all primipara at Yale was abandoned. It is remarkable that there appeared to be no increase in leukemia among the offspring of all these mothers. Thom was not only an expert clinical and academic obstetrician with several inventions of instruments, but also a medical historian and an accomplished artist, lithographer and engraver.

During the early 1950s little gynecologic surgery was practiced or taught at Yale. In 1952, therefore, Dean Hugh Long and Gustave Lindskog, professor of surgery, invited John McLean Morris (Figure 14) to New Haven to remedy this shortcoming. Morris was then in Dr. Meigs’ Department of Gynecologic Surgery at Massachusetts General Hospital in Boston, where he trained together with Drs. Ullfelder, Ingersoll, Langdon Parsons and Summers Sturgis. He spent a year with Hans Kottmeier at the Radiumhemmet in Stockholm and learned that radiation was an alternative to surgery, particularly in the management of cancer of the cervix. For Morris, coming to Yale was an abrupt change from Harvard where gynecology was a separate department related to surgery rather than to obstetrics, and where staff members had full surgical training.

Morris established gynecologic surgery at Yale and created a close link with radiation therapy, a symbiosis that lasted through his lifetime. The standards of excellence and accountability he established are recalled by generations of still-trembling former Yale Ob/Gyn residents. He was responsible, with Chu Chang, for developing the radiation system used at Yale for treating cancer of the cervix. With Meigs he described the distinction between resectable and non-resectable cancer of the cervix that was later included in the FIGO classification of that disease. With Robert Scully he described testicular feminization and, based on the original work of Gertrude Van Wagenen, he helped to develop the “morning-after pill,” so fulfilling a deep interest in population control. John Morris became emeritus in 1985 and died in 1993. A more detailed description of his life and contribution to gynecology is available in the October 2009 issue of Connecticut Medicine (3).

Charles Lee Buxton (Figure 15) succeeded Thom as chairman in 1954. He was an undergraduate at Princeton, obtained his MD from Columbia in 1932, and in 1940 obtained the MedScD degree. Following an internship in Cooperstown and research at Harvard from 1933 to 1934, he did his residency at the Sloane Hospital, New York, and at Columbia. He was invited to the chair at Yale in 1953 at a salary of $22,000 a year. Buxton was what would now be called a reproductive surgeon.

Some of the endocrinologists nurtured by Buxton include Walter Herrmann, who trained in Switzerland, came as an endocrinologist to Yale and went on to become chairman, first in Seattle and then in Geneva, and Raymond Van de Wiele, who...
trained in Belgium and went on to become the endocrinologist at Columbia. Both were pioneers in the investigation of steroid physiology of the ovary. Luigi Mastroianni grew up in New Haven, where both his parents were physicians, went to Yale College for his MD and to Boston University for his residency. He worked with John Rock at Harvard and came to Yale as assistant professor in 1954. Subsequently he became an endocrinologist at the University of Pennsylvania, and then its chair for over 25 years.

Buxton’s greatest contribution was as a visionary who recognized good ideas that had the potential to be realized. He then sought persons with expertise to develop these ideas and thus attracted individuals who initiated research programs in endocrinology, fetal monitoring and diagnostic ultrasound. This was the beginning of subspecialty disciplines in the United States. First Buxton invited Nathan Kase to initiate a Section of Endocrinology. Kase was a graduate of Columbia and, following residency at Mount Sinai in New York, he did a fellowship in steroid biochemistry at the Worcester Foundation. He was a charismatic and exciting teacher of molecular and clinical endocrinology and “could bring the steroid nucleus to life and make it dance.” His Saturday morning lectures were crowded with faculty, residents and students. These lectures resulted in the publication of the now-standard textbook he produced, together with Robert Glass and Leon Speroff.

The second field that Buxton nurtured was fetal electrocardiography. This research had been initia-
was initiated by Professor Wilder Tileston of the Yale Medical School, and the court again upheld the constitutionality of the law. The issue was brought to a head when Dr. Buxton and Estelle Griswold, executive director of Planned Parenthood of Connecticut, opened a birth control clinic in November 1961. Both were arrested. Buxton later remarked that he thought he was worth more than the hundred-dollar bail demanded. Both were fined. The appeal reached the Supreme Court of the United States in October 1965, and the law was overturned. Justice Douglas delivered the majority opinion of the Court with Justices Goldberg and Brandon and Chief Justice Warren concurring.

During Dr. Buxton’s tenure as chair, there were several individuals who came as residents, usually stayed as junior faculty members and then went on to have distinguished careers. Dr. David Gershenson (Figure 18) went to a fellowship with Dr. Felix Rutledge at M.D. Anderson Hospital, stayed on the faculty in gynecological oncology and eventually became chair of that institution. Phillip DiSaia (Figure 19) did his residency at Yale and also went on as a fellow to M.D. Anderson Hospital, becoming director of the division of gynecological oncology at the University of California at Irvine in 1989. He subsequently became chair of the department and Associate Vice Chancellor for Health Sciences, associate dean, and is presently the director of the Gynecological Oncology Group.

Two other notable residents arrived at Yale during the Buxton era. One was Leon Speroff (Figure 20) who graduated from Denison University, Ohio, and went to Case Western Reserve for his MD. While a second-year medical student, he decided he “wanted to be America’s Grantly Dick-Read” (a British obstetrician regarded as the father of the natural childbirth movement). At that time Yale had the only academic department in the United States that promoted natural childbirth. Speroff did a summer clerkship. Subsequently he received a telegram from Dr. Buxton, inviting him to become a resident at Yale. When he arrived, Nathan Kase had just become chair and persuaded him to change and become an endocrinologist. While a resident, he persuaded the hospital to increase the salary for residents from $150 a month to $300 a month, which was still $200 short of the cost of living at that time. Like Kase before him, he went on to the Worcester Foundation and then came back to Yale as assistant professor, subsequently becoming associate professor. He left to become chairman at Case Western Reserve and later professor of obstetrics and gynecology at Oregon Health Sciences University, where he had an exciting and distinguished career.

The second person was Philip Sarrel (Figure 21), another resident during the Buxton era. He went to college at Dartmouth and did a medical internship at Mount Sinai Hospital in New York. During his residency at Yale, he organized a special clinic for unwed mothers that became a national model. His research interests remained in sexuality, contraception and menopause. He was founder of the Yale Menopause Program and the Yale Sex
Counseling Service. He was on the faculty of Gynecology and Obstetrics as well as Psychiatry. He became emeritus in 2009.

Buxton had great personal charm and was a genial and attentive host. Many of us remember with affection the Sunday morning brunches he gave, attended by all members of the staff. He left the Department prepared for subspecialization and ready to absorb the knowledge explosion of the last quarter of the 20th century.

Following a national search, Edward Quilligan (Figure 22) was appointed to the chair of gynecology and obstetrics in 1967. Quilligan obtained his bachelor’s degree and MD from Ohio State University and performed his residency at Case Western Reserve in Cleveland, where he remained on the faculty. When he came to New Haven he worked with Edward Hon, who was at that time establishing fetal electrocardiography as a monitoring methodology during labor. For this research to be statistically valid, a greater number of patients were required than were available in New Haven. Quilligan and Hon therefore moved to the University of Southern California (USC) in Los Angeles, where Quilligan served as chair. Subsequently Quilligan went as chair to the University of Wisconsin and then to the University of California at Davis. He also served as associate vice president of health sciences at UC and then dean at UC Irvine. In 1989 he returned to teaching at UC Irvine Medical Center in Orange. He contributed substantially to the development of the practice of fetal monitoring during labor and showed that fetal distress could be identified at a much earlier stage. The goal was to reduce complications and infant mortality. Subsequently he focused on uterine function in pregnancy, the role of abnormal oxygen levels in fetal brain damage, fetal breathing and fetal sleep states.

When Quilligan left for Los Angeles in 1969, Nathan Kase (Figure 23) was promoted to the chair. As described previously, Kase had been recruited by Dr. Buxton to initiate the section of endocrinology. Kase brought Alan DeCherney (Figure 24) and Donald Coustan to the Department. The initial intent was to initiate a general practice of obstetrics and gynecology within the departments. It soon became clear that this was not an academically profitable venture. DeCherney went on to create the first in vitro fertilization unit in the Eastern United States. He was aided in this venture by Neri Laufer, a graduate of Hadassah Medical School in Jerusalem, who was then working in the Biology Department at Yale with Professor Clement Markert. This unit has since become one of the leading departments of in vitro fertilization in the country. DeCherney went on to become professor and chair of obstetrics and gynecology at Tufts University School of Medicine in Boston. Then he became chair and director of reproductive endocrinology at UCLA and subsequently moved to Washington to become head of the Program in Reproductive Endocrinology at the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health. He was elected a member of the Institute of Medicine of the National Academies in 2004.
Donald Coustan (Figure 25) became a perinatologist, particularly interested in diabetic pregnancy. He went on to become chair at Brown Medical School and became a national authority on diabetic pregnancy.

In the fifth Lee Buxton Memorial Lecture in 1990, Nathan Kase described how he saw the Department during the previous 20 years. He came to Yale in 1962 with a salary of $8,000 a year. This was raised to $11,000 when he received his first research grant. “At that time,” he said, “it was possible to combine research and teaching with a defined subspecialty clinical practice. Obstetrics and gynecology was in the midst of a transition from one being a professor ‘of all things’ to an emphasis on the subspecialty in perinatology or oncology or endocrinology. There was an explosion of knowledge; in 1962 pregnancy tests were done by the rabbit assay. Two years later there was immunoassay. Obstetrics and gynecology had become reproductive science. We could follow clinical and research interests as shareholders and partners in the intellectual enterprise. We could develop new areas of expertise. There were really no bosses to tell us what to do. The salary was that of civil servants, but there was little constraint on our intellectual effort. Those were the 1960s and 1970s.”

John Hobbins (Figure 26) returned to the faculty soon after Kase became chair. He had graduated from Hamilton College and New York Medical College and completed his residency at Yale prior to military service. He was recruited to initiate the division of perinatology. Besides fetal ultrasound diagnosis, Dr. Hobbins developed fetoscopy and the in-utero diagnosis of haemoglobinopathies. He made possible the prenatal diagnosis of Ellis-van Creveld syndrome and of Duchenne muscular dystrophy. He established intraperitoneal and subsequently perfected intravascular fetal transfusions. Dr. Hobbins is regarded as a “formidable teacher” and trained many of today’s leaders in the field, including Roberto Romero, E. Albert Reece and Joshua Copel, among many others. He moved to the University of Colorado in Denver in 1992.

Peter E. Schwartz (Figure 27) was recruited to Yale to initiate a section of Gynecologic Oncology. He had graduated from Union College and Albert Einstein College of Medicine, did his residency at Yale and was advised to go to M.D. Anderson Hospital for fellowship in gynecologic oncology.
When Dr. Morris stepped down as chief of gynecology, Schwartz established the oncology section and the training fellowship. His major interest has been the early diagnosis of ovarian cancer and the use of “prophylactic” chemotherapy in the initial management of advanced ovarian cancer. His introduction of chemotherapy for germ cell tumors has preserved the fertility of many generations of affected young women.

Kase also brought Harold Behrman (Figure 28) and Richard Hochberg (Figure 29) to Yale, both reproductive scientists who established laboratories that have made major significant contributions to that science.

But all was not perfect. Robert Glass was remarkable in that he went to Yale College and Yale School of Medicine and then remained on the faculty for 10 years. When he was to be promoted to full professor, the medical school had financial problems and there were no funds for promotion in any department in the medical school. This was because of the University rule that any tenured professor had to have set aside sufficient funds in the endowment of the University to pay for the length of the professorship. To solve this problem, the University created a class of “clinical” professors. Such persons did not have tenure in the traditional sense of the word but had a “continuing appointment” that could not be terminated except if the whole class of such professors was terminated. Glass felt betrayed and left Yale to become a professor at the University of California, San Francisco.

Nathan Kase left Yale after eight years as chair in 1977 to become chairman at his alma mater, Mount Sinai Medical School in New York, where he subsequently became dean and had a further distinguished career.

Frederick Naftolin (Figure 30) was appointed Kase’s successor in 1978 and remained as chair for 23 years, nearly rivaling the 28-year tenure of Dr. Morse. Naftolin had graduated from the University of California at San Francisco and had obtained a D. Phil. degree from Oxford University, working with Geoffrey Harris, the discoverer of the pituitary portal system. He had spent time at Harvard and at the time of his move was chairman of the Department of Obstetrics and Gynecology at McGill in Canada. A member of his faculty recently said, “Naftolin’s greatest contribution was his passion for research of any sort. He allowed academic freedom wherever it would lead, even outside the traditional gynecology obstetrics field. That’s how we ended up in neuroscience in our department. We could pursue our dreams and excellence wherever they would lead.” After retirement, he left Yale to become director of biologic research in the Department of Obstetrics and Gynecology at the New York University School of Medicine where he is at present.

Dr. Charles Lockwood (Figure 31) became chairman in 2002. He had received his undergraduate education at Brown University, his medical training at the University of Pennsylvania, served
a residency at Pennsylvania Hospital and a Maternal-Fetal Medicine fellowship at Yale under John Hobbins. After a two-year sojourn at Tufts, he completed a postdoctoral fellowship under Yale Nemerson at Mount Sinai in molecular hemostasis, where he stayed on the faculty until 1995. He became chairman at New York University that year. During his present tenure, the faculty number has increased to 59 persons, and the Department is thriving under his tutelage.

It is noteworthy that many of the residents who came to Yale with academic ambition decided to go into clinical practice rather than pursue a professorial career. Conversely, many who entered residency with a view toward clinical practice were so stimulated by the enthusiastic atmosphere encouraging research that they became academicians. Frequently this was quite a dramatic transformation. It should also be noted that many of the graduates of the residency program went into private practice in New Haven and surrounding towns and played a significant role in resident and medical student teaching.

**LOOKING BACKWARD, LOOKING FORWARD**

What has changed in obstetrics and gynecology in the last 40 years? The clinician scholar professor track has become routine for all clinicians, and most clinical departments reserve tenure-track professorships for their research faculty. Soon after his appointment, Dr. Naftolin tried to obtain a clinical professorship for himself, but it appeared he would lose status and the respect of other chairpersons. He therefore had to retain his tenure-track professorship. A clinician educator track has been instituted also, to try and encourage good teaching in the medical school.

There is no doubt that the enthusiasm for research and teaching continues to fulfill the ambition of many of those who rise through the ranks of professorships and infuse that spirit into the medical students. Research grants 50 years ago were not too difficult to obtain. In spite of the present national fiscal problems and tight NIH pay lines, the Department’s research operation has grown markedly in size and international stature in the last nine years and is academically very successful. In 1964, Dr. Buxton had a faculty of eight and one administrative secretary. In the past eight years the Department has grown to 59 clinical and research faculty, 25 postdoctoral research fellows, 16 clinical fellows and 97 clerical, technical and managerial staff. Research funding in FY2011 is projected to exceed $16 million with nearly $11 million in total NIH dollars.

What is of concern is that the teaching of medical students and even residents has become more challenging and difficult. Patients spend little time in the hospital as inpatients, and there is less time for them to meet medical students. The leisure of outpatient teaching has largely disappeared so that the opportunity to learn by example has become a luxury. I do not believe that one can teach clinical medicine by computer modeling. The emphasis on throughput, patient safety, patient satisfaction, expense reductions and revenue generation, so prevalent in medicine today, makes good clinical teaching a challenge. This is the most urgent problem of medical schools in the United States at the present time. Our physicians are so busy, both in academic and in private practice, that there is even little time to come to Grand Rounds. That surely can be fixed!

However, the future is bright! There are many star players in our Department at the present time, and their achievements will surpass and certainly rival those of all previous generations.
REFERENCES


To view Dr. Kohorn’s article in its entirety, please visit: http://medicine.yale.edu/obgyn/yogs/87_179521_Kohorn_Smith_Buxton.pdf *

To view Dr. Gross’s article on Griswold v. Connecticut, please visit: http://medicine.yale.edu/obgyn/yogs/87_179528_Gross_Griswold_CT.pdf **

* Presented at Grand Rounds, Department of Gynecology & Obstetrics, January 2011. The portion of this history from 1800 to 1965 has been reproduced with permission of the Yale Journal of Biology and Medicine (copyright 1993). It has been abridged and revised. The text since that time is original.

** The original version of this article was first given as a speech at the ABCD-sponsored 40th anniversary celebration of the Griswold v. Connecticut decision held at the Massachusetts State House in March 2005. It was modified for presentation at the June 7, 2005 celebration held at the Senate Office Building. The article was further modified for presentation at Yale Ob/Gyn Grand Rounds in 2005 and presented at the Beaumont Society on March 17, 2006. We are publishing this article in honor of Yale’s 200th anniversary and the 50th birthday of the approval of oral contraceptives for contraceptive purpose in the United States.
Preconception/Interconception Counseling and Care

Prenatal care should begin in the preconception period with risk assessment being the primary objective for preconception education (1). Preconception education is important because evidence suggests that women who plan pregnancy are more likely to have a healthy birth outcome. This is particularly relevant because the leading causes for infant mortality in the United States are congenital anomalies, preterm birth, low birth weight and chronic medical disease morbidities complicating pregnancy. Unfortunately, only 50% of pregnancies in the United States are planned, which is directly related to high infant mortality and racial disparity in infant mortality compared to other developed countries.

The definition posed by the Center for Disease Control (CDC) for preconception care is intervention that aims to identify and modify biomedical, behavioral and social risks to a woman’s health through prevention and management. Interconception care is the time period between pregnancies, which is generally about 18 to 24 months postpartum, where the woman can direct her attention to healthier lifestyle goals to improve upon pregnancy outcomes.

The important elements to effective preconception care include screening for medical and social risk factors, providing appropriate immunizations, counseling based on medical and genetic history, age and ethnic risk, health education and interventions such as weight loss and control of diabetes and blood pressure, known to improve pregnancy outcome and overall adult health.

Immunization status should be evaluated for rubella, varicella, hepatitis B and diphtheria, tetanus, pertussis (Tdap vaccine). Infections with potential risk to the fetus include cytomegalovirus (CMV), toxoplasmosis, parvovirus and HIV. For some women in high-risk situations, the immunization for CMV and parvovirus may be appropriate. HIV testing is a routine component of prenatal laboratory testing. Women with preexisting medical conditions should receive counseling prior to pregnancy to understand the risk of those conditions on their health and the health of the fetus. For example, in the U.S., obesity is the leading chronic disease of reproductive-age women; chronic hypertension occurs in 22% and diabetes in 7%.

COUNSELING ON SPECIFIC CONDITIONS

DIABETES
Uncontrolled pregestational diabetes is associated with increased risk for congenital anomalies, specifically heart and neural tube defects, stillbirth and birth trauma. The pregestational diabetic should aim to optimize diabetes control prior to conception. The goal should be to have a hemoglobin A1C level <6.5%. A hemoglobin A1C level >6% is associated with a 15% to 20% increased risk for miscarriage and a 5% to 10% risk for birth defects. Also, renal function should be assessed because of maternal risk for preeclampsia, and an ophthalmological examination should be performed to evaluate for retinopathy so that appropriate treatment can occur for this condi-
tion prior to pregnancy. The patient should be educated with the goal of maintaining euglycemia with whatever regimen she is using to control diabetes. The objective is a fasting blood sugar level <100 mg/dl and two-hour postprandial blood sugars <120 mg/dl. These patients should also be on a vitamin with folic acid supplementation prior to conception and maintain a folate-rich diet.

**HYPERTENSION**

Women with chronic (essential) hypertension are at increased risk for stroke, renal and cardiovascular compromise and preeclampsia. Pregnancy complications associated with chronic hypertension are placental abruption, fetal growth restriction and stillbirth. Women with chronic hypertension should have a baseline renal function evaluation and review of medication. ACE inhibitors should be avoided during pregnancy because of the risk for congenital renal tubular dysplasia. The goal for blood pressure control is <140/90 mmHg with a single medication. Commonly used medications for control of hypertension are beta blockers and calcium channel blockers.

**SEIZURE DISORDER (EPILEPSY)**

Women with seizure disorders controlled with medication should be counseled on medication risk for birth defects. All medications used for seizure control have some risk for causing birth defects, and the benefits for seizure control must be weighed against the risk for the medications. The patient should be counseled that medications may need to be adjusted upward in order to maintain seizure control. The goal is to adjust or reevaluate the need for medications to those with the lowest risk. Valproic acid, in particular, is associated with increased risk for neural tube defects and cardiac defects. All women with a history of seizures should be on a vitamin containing folic acid.

**OBESITY**

Women who are overweight or obese should be aware of the increased risk for birth defects, medical complications of pregnancy including preeclampsia and gestational diabetes, and the risk for cesarean delivery. It is recommended that women aim to establish and maintain a normal body mass index (BMI) prior to pregnancy and follow the Institute of Medicine (IOM) guidelines for weight gain during pregnancy (2). A derivative study of the FASTER Trial, evaluating the link between obesity and cesarean delivery, noted that women classified as morbidly obese had a risk for cesarean delivery of 47.4% (3).

Interconceptionally, obese women should aim to create a healthy lifestyle with diet and exercise to achieve a healthier weight prior to the next pregnancy. They should recognize the benefits of breastfeeding to themselves and their infant for long-term health. Breastfed infants have a lower risk for adult cardiovascular disease and obesity.

**HEART DISEASE**

Adult heart disease puts the patient at risk for pregnancy morbidity and mortality. Specifically, women with corrected congenital heart disease have a risk for recurrence of congenital heart defects in offspring. Uncorrected adult congenital heart disease can result in decompensation due to physiological increase in plasma volume during pregnancy. Women with artificial heart valves, specifically mechanical valves, typically require Coumadin to prevent thromboembolism.

However, Coumadin is teratogenic, and women with mechanical valves contemplating pregnancy must be apprised of the risk for thromboembolism if Coumadin is discontinued in favor of heparin during early embryogenesis. Prior cardiomyopathy should be considered a contraindication to pregnancy because of the increased risk for mortality.

**OTHER CONDITIONS**

Women with collagen disease and thyroid conditions should also be counseled for potential morbidity and should be advised of any medication risk prior to conception.

**THE INFERTILE COUPLE**

Approximately 15% to 20% of couples of reproductive age have difficulty conceiving. The patient and her partner must appreciate any preexisting medical conditions that pose a risk to mother or fetus. All women should be aware of the increased risk for multiple gestations with ovulation.
induction or in vitro fertilization. Advanced maternal age is often a factor for the infertile female, and the risk for aneuploidy should be discussed prior to conception. All women undergoing infertility treatment should be on a vitamin containing folic acid prior to conception.

FOLIC ACID RECOMMENDATIONS
In 1992 the U.S. Public Health Service advised a vitamin containing folic acid for all reproductive-age women to reduce the risk for neural tube defects and for improvement of overall pregnancy outcome. In 2004, only 40% of reproductive-age women reported taking a vitamin with folic acid. Preconception recommendations are for at least 400ug of folic acid daily beginning four weeks prior to conception and continuing for the first three months of pregnancy. The women should also maintain a folic-rich diet prior to conception and throughout pregnancy.

DRUGS AND MEDICATIONS
A number of drugs that are taken for medical conditions are known to pose a teratogenic risk to the developing embryo. Some specific drugs include valproic acid, Coumadin, isotretinoin and lithium. The patient should be advised of the risk of alcohol and to avoid cigarette smoking and illicit drug use.

There are a number of teratogen information services and computer databases to consult that provide appropriate counseling to women, including MICROMEDEX, REPROTOX (Reproductive Toxicology Center) and TERIS (Teratogen Information Service).

There is no evidence that caffeine or aspartame (Nutrasweet) is teratogenic. One study showed that heavy use (>300 mg/day; >8 cups of coffee) increased risk for stillbirth (OR 3.0, CI 1.5-5.9) (4).

PREGNANCY AFTER PREGNANCY LOSS
There are no good data on appropriate timing to optimize pregnancy outcome after pregnancy loss. Each patient should be evaluated about grief response and should begin trying for the next pregnancy when she is ready.

THE EXPECTANT FATHER (PARTNER)
The partner should be involved in preconception counseling. Partner involvement leads to a healthier birth outcome. The partner should also appreciate the long-term health benefits of breastfeeding for mother and child. A study by Arora and associates (5) indicated that 40% to 75% of women reported that their partners’ opinion or preference impacted their decision about breastfeeding.

SUMMARY
Prenatal care should begin in the preconception period to counsel and address health concerns that can impact mother and child. All women contemplating pregnancy should begin a multivitamin supplemented with folic acid at least four weeks prior to conception.

REFERENCES:


Management of recurrent spontaneous abortion (SAB) is quite challenging. Affected patients are often offered non-evidence based or anecdotal treatments, there is no consensus on definitions, and prevalence estimates are confounded by the high background rate of pregnancy wastage. It is generally accepted that 1% of couples suffer two or more consecutive pregnancy losses prior to the third trimester (1).

At least half of sporadic SABs have aneuploid karyotypes, most commonly trisomies, followed by polyploidy and monosomy X (2). Maternal age is strongly associated with the risk of both SAB and aneuploidy. One prospective cohort study of over 36,000 women examined relative miscarriage and aneuploidy rates in three age groups: less than 35 years, 35–39 years, and 40 years or older (3). Multivariate logistic regression adjusting for potential confounders determined that, compared to women <35 years, those 35–39 years old had an increased risk for SAB with an adjusted odds ratio (adjOR) of 2.0 (95% confidence intervals, 1.5–2.6) while those ≥40 years of age had an adjOR of 2.4 (95% CI, 1.6–3.6) for SAB. Moreover, the association of embryonic chromosomal abnormalities with these two age groups produced adjORs of 4.0 (95% CI, 2.5–6.3) and 9.9 (95% CI, 5.8–17.0), respectively. A second larger Scandinavian prospective cohort study of 634,272 women having 1.2 million pregnancies found progressively higher SAB rates with increasing maternal age: <12% for women 20–29 years, 15% for those 30–34 years, 24.6% for those 35–39 years, 51% for ages 40–44 and 93.4% for women ≥45 years (4).

While there is no universally accepted explanation for why aneuploidy is associated with advanced maternal age, former Yale Ob/Gyn resident and fellow, David Keefe, now chair of Ob/Gyn at New York University, has posited that progressive shortening of oocyte telomere length due to the cumulative effects of oxidative stress may be the culprit (5). Such shortening of telomere can lead to abnormal chiasma formation and, hence, nondisjunction.

**GENETIC CAUSES**

Between 25% and 57% of patients with recurrent SAB have recurrent aneuploid conceptuses (6, 7). Patients with recurrent miscarriage undergoing in vitro fertilization (IVF) with preimplantation genetic testing have far higher rates of abnormal embryos compared with controls (70.7% vs. 45.1%; P <0.0001) (8). Given the link between advanced maternal age and aneuploidy, it is not surprising that recurrent SAB patients are significantly older than the general obstetric population (9). Thus, as with sporadic SABs, oxidative stress-induced reductions in oocyte telomere length may be a causative factor (5). Another hypothesis put forth has been skewed inactivation of the X chromosome, causing either nondisjunction or unmasking of an X-linked dominant or germ line developmentally lethal mutation on the X chromosome. However, recent studies have refuted such an association (10, 11).

Potential treatments for recurrent aneuploidy are speculative at best. Low folate levels have been linked to miscarriage when the fetal karyotype is abnormal (OR of 1.95; 95% CI, 1.09–3.48) but not when the fetal karyotype is normal (OR 1.11; 95% CI, 0.55–2.24) (12). Thus, it would seem prudent to treat patients experiencing recurrent SAB with periconceptional folate supplementation. A second strategy proposed for patients with recurrent miscarriage resulting from advanced maternal age-related aneuploidy is IVF with preimplantation genetic screening (PGS) for trisomies commonly found in abortus specimens. However, randomized controlled trials examining outcomes of IVF with PGS for common aneuploidies in women of advanced reproductive age have not demonstrated any benefit (13, 14).

A 30-fold increased occurrence of balanced translocations has been found among couples with recurrent miscarriage with a prevalence of 3.6% (15). Affected couples experience up to a 29% SAB rate, with 36% of the abortuses found to have an unbalanced translocation (16). For this reason high-resolution parental karyotyping should be performed in couples with unexplained recurrent early SAB. It is unclear whether IVF with PGS reduces loss rates in couples with balanced translocations and recurrent loss (17).

Mendelian or single gene defects may also contribute to recurrent SAB, including X-linked and autosomal recessive disorders or germ line mutations involving loss of heterozygosity. Advances in whole genomic sequencing now permit the sequencing of SAB samples to discover putative single gene causes. At Yale, the cost of such screening is $2,000, nearly comparable to the cost of karyotyping the products of conception. This approach will likely identify mutations in developmentally relevant genes such as those in the Tbx, HOX, SOX and FOX gene families. Alternatively, future studies may find that methylation defects in the promoter regions of these genes are common causes of aberrant development. For couples without such financial resources or when no fresh abortus specimen is available for sequencing, evaluation of the placental histology may provide clues as to the presence of developmental abnormalities, including the presence of trophoblast inclusions, abnormal invaginations of the villous surface which on section appear as inverted islands of trophoblast (18). This service is provided at Yale by Dr. Harvey Kliman in our Department.

INFECTIONOUS DISEASES

While acute severe bacterial, parasitic and viral infections can cause sporadic SABs, there are no unequivocal data establishing an association between chronic genital tract carriage of bacteria and recurrent miscarriage. Moreover, there is no evidence that the presence of Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, human cytomegalovirus (HCMV), adeno-associated virus (AAV) and human papillomaviruses (HPV) is associated with even isolated first trimester SAB (19). There is also no significant association between recovery of genital tract Chlamydia trachomatis or the presence of antichlamydial antibodies and recurrent SAB (20). Furthermore, while bacterial vaginosis (BV) has been associated with SAB (adjOR 2.67; 95% CI, 1.26–5.63) (21), this association appears more robust with second rather than first trimester pregnancy loss (22).

CELIAC DISEASE

There is growing evidence of a link between clinically apparent celiac disease and recurrent SAB. Kotze reported a higher prevalence of SABs among 76 adult celiac patients vs. 84 adult controls with irritable bowel syndrome (24.4% vs. 11.6%) (p = 0.003) (23). Furthermore, he observed that pregnancy outcomes improved in 12 celiac patients after treatment with a decrease in SABs from 38.9% to 5.6%) (p = 0.045). Other investigators have made similar observations (24, 25). Therefore, symptomatic celiac disease appears to be associated with multiple SABs, and treatment appears to improve live birth rates.

ENDOCRINOPATHIES

Poorly controlled diabetes is a well-known cause of recurrent SAB. However, there is no evidence that subclinical diabetes causes recurrent miscarriage (26). However, patients with recurrent SAB more commonly display antithyroid peroxidase and anti-thyroglobulin antibodies (27). Moreover, non-randomized studies have suggested that
levothyroxine therapy may decrease SAB rates in euthyroid antibody positive women (27). In contrast, recent studies have found no link between polycystic ovarian syndrome (PCOS) and recurrent SAB (28, 29). In addition, Legro and associates randomized 626 infertile PCOS patients to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to six months, and observed live birth rates of 22.5%, 7.2% and 26.8%, respectively; the rate of SABs was not different among the groups (30). Thus, screening for PCOS and treating affected patients with metformin do not seem appropriate in the management of patients with recurrent SAB.

Progesterone plays a crucial role in the maintenance of endometrial hemostasis while the anti-progestin RU 486 can induce menstruation and early abortion by inhibiting these salutary effects of progesterone (31-33). These studies provide biological plausibility for the theory that luteal phase defects could promote early pregnancy loss. However, recurrent SAB patients with documented luteal phase defects actually have lower recurrent SAB rates than those without such a defect (34). Moreover, meta-analysis of trials of progesterone therapy for recurrent miscarriage has not demonstrated a benefit (35).

In contrast, patients with recurrent SAB and hyperprolactinemia have improved live birth rates following treatment with bromocriptine (36). Thus, it may be useful to obtain prolactin levels in such patients, and a trial of therapy in hyperprolactinemic women with recurrent SAB may improve live birth rates.

UTERINE ABNORMALITIES
The link between uterine structural abnormalities and recurrent loss has been suggested by small case-control studies. A number of theories have been suggested to account for a putative association between uterine anomalies and recurrent SAB, including decreased vascularity in the septum, increased inflammation and a reduction in sensitivity to steroid hormones (37). However, there are also no controlled randomized clinical trials of pregnancy outcome following resection of the uterine septum. Moreover, open metroplasty is rarely recommended for bicornuate or didelphys uteri due to the attendant risks of infertility and uterine rupture during pregnancy, as well as the more favorable associated pregnancy outcomes in patients with these defects. Submucous myomas that distort the uterine cavity have been posited as causes of recurrent miscarriage and reduced IVF success rates, and hysteroscopic resection may improve fertility and live birth rates (38, 39). Asherman syndrome and polyps have also been posited as causes of recurrent SAB, and descriptive series suggest improvements in pregnancy outcomes following hysteroscopic resection (40). Thus, patients with recurrent SAB should be screened for uterine defects by sonohysterography. Subsequent 3-D ultrasound, available at our Long Wharf site, can allow differentiation of bicornuate from septate uteri without resorting to expensive MRI imaging.

INHERITED THROMBOPHILIAS
The association between inherited thrombophilias and recurrent SABs has been suggested by small case-control studies. Meta-analysis of 31 studies reported a modest link between factor V Leiden (FVL) and first trimester SAB with OR of 2.01 (95% CI, 1.13–3.58) but a stronger association with late (>19 weeks) non-recurrent fetal loss (OR 3.26; 95% CI, 1.82–5.83) (41). A second meta-analysis of the link between FVL and adverse pregnancy events noted no association with first trimester losses but a strong association with two or more second or third trimester fetal losses (OR 10.7; 95% CI, 4.0–28.5) (42). Similarly, a large European retrospective cohort study compared pregnancy outcomes among 571 women with thrombophilias having 1524 pregnancies, compared with 395 controls having 1019 pregnancies, and reported an association between inherited thrombophilias and stillbirth (OR 3.6; 95% CI, 1.4–9.4) but not with SAB (OR 1.27; 95% CI, 0.94–1.71) (43). However, more recent prospective studies have not shown an association between FVL and other common inherited thrombophilias with SAB, stillbirth and other adverse pregnancy outcomes (44-48). Thus, retrospective studies do not demonstrate an associa-
tion between inherited thrombophilias and early (<10 weeks) pregnancy loss, and prospective studies in low-risk populations do not suggest an association between inherited thrombophilias and later losses.

In addition, it is unclear that anticoagulation therapy prevents recurrent fetal loss among such patients. Kaandorp and associates conducted a randomized clinical trial among 364 women with a history of unexplained recurrent SAB, comparing 80 mg of aspirin plus open-label LMWH (nadroparin), 80 mg of aspirin alone, or placebo, observed no difference in live birth rates among the three study groups (54.5%, 50.8% and 57.0%, respectively) and found no significant benefits among the 16% of women with inherited thrombophilia (49).

Given these findings, there is no apparent value to establishing the diagnosis of inherited thrombophilia in patients with recurrent early pregnancy loss. There is also no consensus on the utility of such evaluations among patients with later pregnancy losses and other adverse pregnancy outcomes. Finally, there is no clear evidence that treatment with anticoagulation drugs improves pregnancy outcomes among such patients.

ANTIPHOSPHOLIPID ANTIBODIES
Antiphospholipid antibody (APA) syndrome is defined by the combination of a prior deep venous or arterial thrombosis, characteristic obstetric complications, or thrombocytopenia coupled with laboratory confirmation of APA (50). The latter criteria include: medium to high titer IgG or IgM anticardiolipin antibodies (ACA), IgG or IgM anti-β2-glycoprotein-I (a β2GPI) antibodies at levels ≥99th percentile, or the presence of a lupus anticoagulant (LAC). These APAs must be found on two or more occasions at least 12 weeks apart. Obstetric complications include at least one fetal death at 10 weeks’ or more gestation, at least one preterm birth before 35 weeks, or at least three consecutive SABs before the 10th week. All other causes of pregnancy morbidity must be excluded. The APAs are immunoglobulins directed against proteins bound to negatively charged (anionic) phospholipids. They can be detected by screening for antibodies binding directly to protein epitopes (e.g., β2-glycoprotein-1, prothrombin, annexin V), by indirectly detecting antibodies reacting to proteins present in an anionic phospholipid matrix (e.g., cardiolipin and phosphatidylerine) or by evaluating the “downstream” coagulation effects of these antibodies on in vitro prothrombin activation (i.e., lupus anticoagulants) (51).

Five to 15% of women with recurrent SAB have documented APA compared with 2% to 5% of the general obstetrical population (52). The presence of LAC is associated with ORs of 3.0–4.8 for fetal loss while the presence of ACA has ORs of 0.86–20.0 for fetal loss (53). These antibodies are more strongly associated with fetal rather than embryonic loss. Indeed, compared with patients having unexplained first trimester losses without APA, those with antibodies more often have documented fetal cardiac activity prior to a loss (86% vs. 43%; p <0.01) (54). In addition, meta-analysis of seven studies reported no significant association between APA and either clinical pregnancy (OR 0.99; 95% CI, 0.64–1.53) or live birth rates (OR 1.07; 95% CI, 0.66–1.75) in patients undergoing IVF (55).

Treatment of affected patients requires both low molecular weight heparin (LMWH) and low dose aspirin. Mak and associates performed a meta-analysis of randomized clinical trials, comparing the efficacy of unfractionated heparin or LMWH plus aspirin to aspirin alone in patients with APA and recurrent pregnancy loss (56). Five trials involving 334 patients were available for analysis, and live birth rates between the two treatment groups were 74.3% and 55.8%, respectively.

IMMUNOLOGIC CAUSES
A link between elevated circulating natural killer (NK) cell activity and recurrent SAB has been suggested by several small studies. The underlying theory is that excess decidual NK cell activity may damage the implanting blastocyst or re-range early placentation to promote miscarriage. Yamada and colleagues reported that elevated peripheral blood preconception NK cell activity (>46%; relative risk [RR] 3.6; 95% CI, 1.6–8.0) and percentages of circulating NK cells (>16.4%;
RR 4.9; 95% CI, 1.7–13.8) predicted subsequent pregnancy loss with a normal karyotype among SAB patients (57). However, these findings have not been replicated by other investigators (58). Moreover, it is now understood that measurement of circulating NK cell activity is unlikely to provide insights into the decidual NK cell phenotype. We have shown that the mRNA repertoire of circulating NK cells is far different from that of decidual NK cells (59), calling into question the biologic plausibility of measuring peripheral blood NK cell activity as a proxy for decidual and placental bed NK cell activity. In addition, there is evidence that decidual NK cells are actually crucial to normal endovascular trophoblast invasion despite bearing potentially cytotoxic factors (60).

However, abnormal interactions between decidual NK cells and trophoblast antigens may have the potential to activate this cytotoxic capability and promote aberrant placentation. Decidual NK cells in the placental bed express killer-cell immunoglobulin-like receptors (KIR) that can bind to human leukocyte antigen (HLA)-C molecules on trophoblast cells, a process that normally triggers elaboration of salutary growth and angiogenic factors from NK cells that promote trophoblast invasion. In contrast, the presence of KIR AA haplotypes on decidual NK cells, particularly the activating KIR for HLA-C2 groups (KIR2DS1), coupled with HLA-C2 bearing trophoblast, may modestly promote both preeclampsia and recurrent loss (61,62). This is an active area of research in our Department. However, at this point there is absolutely no support for measuring circulating NK cell activity in patients with recurrent abortion or for treating those with putatively increased activity.

EVALUATION OF COUPLES EXPERIENCING RECURRENT SAB:
While there are little evidence-based data to guide the work-up and treatment of patients with recurrent miscarriages, identification of possible genetic factors seems justified. Thus, parental karyotypes and aggressive karyotyping of abortus specimens would appear to be reasonable diagnostic studies. Assessment of placental pathology for trophoblast inclusions may be particularly useful when no prior abortus karyotype was obtained and when there are intermittent euploid losses at around the same gestational ages. In the near future, sequencing the genome of abortus specimens will likely become an option, and this process will undoubtedly identify X-linked, autosomal recessive and germ line loss of heterozygosity for developmentally lethal mutations. Treatment of patients with recurrent aneuploidy losses should include nutritional supplementation with folate. However, the utility of IVF with PGS for common aneuploidies remains an unproven strategy in patients with recurrent aneuploid losses.

It remains a standard approach to search for uterine anatomic abnormalities in such patients with sonohysterography and 3-D ultrasound. Remediable defects should be corrected prior to attempting a subsequent pregnancy. A prolactin level should be obtained, and those found to harbor hyperprolactinemia should be treated with bromocriptine. In contrast, there is no consensus on the utility of screening for anti-thyroid antibodies and treating affected patients with thyroxine supplementation. Finally, a work-up for APA antibodies should be performed in unexplained cases and treatment given to patients with bona fide APA syndrome with LMWH and low dose aspirin.
REFERENCES


Polycystic Ovary Syndrome (PCOS): New Approaches to an Old Entity

OBJECTIVES:

1. Review the diagnostic criteria for PCOS
2. Review the pathophysiology of the disorder
3. Provide an overview of the health implications of PCOS
4. Provide an overview of management paradigms

1. PCOS is the most common endocrinopathy of the reproductive years (1). The prevalence of the disorder ranges from 5%–11% depending upon the population studied; despite being liberally diagnosed, the disorder remains relatively poorly understood. Currently, at least three nomenclatures are recognized to identify affected patients (2, 3); notable is the considerable overlap of diagnostic criteria (Table 1). It is imperative to appreciate that PCOS remains a diagnosis of exclusion; common systemic disorders (e.g., hypothyroidism, hyperprolactinemia, late onset congenital adrenal hyperplasia, androgen secreting tumors, Cushing’s syndrome and exogenous androgen exposure, to name a few) may mimic symptoms and signs of PCOS and must be excluded prior to arriving at this diagnosis.

Symptomatology of PCOS is fairly restrictive and includes menstrual irregularity and symptoms of androgen excess (excessive facial and body hair, acne and occasionally androgenic alopecia). Menstrual irregularity may be acknowledged by up to two thirds, mostly presenting as oligomenorrhea (duration of cycles >35 days) or amenorrhea. Bothersome hair and/or acne may similarly be acknowledged in up to two thirds of the patient population; androgenic alopecia is the least common of the hyperandrogenemic symptoms,

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Hyperandrogenism and/or hyperandrogenemia</td>
<td>+</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>PCO appearance of ovaries on ultrasound</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Diagnostic requisites</td>
<td>Oligomenorrhea</td>
<td>Any two criteria</td>
<td>Hyperandrogenism and/or hyperandrogenemia plus ovulatory concerns (oligomenorrhea or PCO appearance of ovaries on US) - Polycystic appearance of ovary: volume &gt;0ml and/or &gt;12 follicles &lt;9mm in size in at least one ovary</td>
</tr>
</tbody>
</table>
seen in fewer than 10% of patients diagnosed with PCOS. Overweight to obese body habitus may be evident in almost two thirds of cases, whereas the remainder have a normal body mass index (BMI).

2. The pathophysiology of PCOS is far from completely understood. The endocrine profile of PCOS includes an elevation in serum levels of luteinizing hormone (LH) in comparison to follicle stimulating hormone (FSH) levels; hyperandrogenemia is commonly of ovarian origin (elevated testosterone) although elevations in serum levels of dehydroepiandrosterone sulfate (DHEAS) may additionally be seen, suggesting an adrenal contribution to androgen excess in a subset. Mild elevations in prolactin may be observed in a proportion of patients with PCOS. Excess BMI, insulin resistance, dyslipidemia (particularly suppressed HDL levels) and systemic inflammation are hallmarks of the metabolic milieu of PCOS.

3. Clinical concerns relating to the diagnosis of PCOS extend well beyond the presenting symptoms (4). Menstrual irregularity and cosmetic issues dominate in the adolescent and the young, whereas anovulatory infertility adds to the patient’s burden for the reproductive-age population. The risk for endometrial pathology is real and independent of age; a spectrum of proliferative endometrial disorders has been described in women with PCOS, ranging from endometrial polyps to endometrial hyperplasia to adenocarcinoma. This population is at a particularly enhanced risk for chronic medical disorders, particularly type II diabetes, which can be unmasked on provoked testing (e.g., oral glucose tolerance test) in up to 5% of the young women with PCOS, whereas impaired glucose tolerance may be seen in up to one third of patients on provoked testing. Cross-sectional studies identify PCOS as a risk for cardiovascular disease (CVD). A disproportionally increased prevalence of depressive symptomatology is also described in women with PCOS. While the prognosis for reproductive success with fertility treatment is reassuring, these patients are at an increased risk of complications relating to infertility treatment, including risk for ovarian hyperstimulation syndrome, multiple pregnancy and spontaneous miscarriage. Reproductive challenges continue for those attaining pregnancy in the form of increased risks for gestational diabetes, preeclampsia and fetal macrosomia. Limited data identify trans-generational implications of this diagnosis.

4. Management strategies must be individualized to the patient’s needs and risk profile. Menstrual regulation may be achieved through use of combined hormonal contraceptive formulations (pills/patch or vaginal ring); this strategy offers endometrial protection as well as benefits against symptoms of androgen excess. Dose of estrogen (higher estrogen dose confers potential for benefit against hyperandrogenemia by increasing the hepatic production of sex hormone binding globulin that binds and reduces the circulating free androgen levels) and type of progestin (antiandrogenic progestins such as drospirenone offer potential for benefit whereas androgenic progestins such as levonorgestrel may worsen symptoms of acne for some) are considerations when deciding on the optimal hormonal contraceptive strategy. Insulin sensitizers offer a potential for improving reproductive physiology (menstrual regulation and improved androgen profile and symptoms of hyperandrogenism) in addition to their metabolic benefit. Combination therapy (OCP + insulin sensitizer) may offer enhanced benefits for individual patients. Statins have shown promise in improving androgen profile and may be of particular benefit for those with significant dyslipidemia in the setting of a strong family history of CVD. Antiandrogen therapies such as spironolactone (Aldactone) and flutamide or finasteride (Propecia) are of particular relevance for the management of signs of hyperandrogenism; adequacy of contraceptive coverage must be ensured when prescribing anti-androgens, given their potential for teratogenicity, especially for male fetuses. Topical eflorenithine (Vaniqa) may be complemented with depilatory strategies for the control of hirsutism, and anti-acne therapies as well as topical vasodilators such as minoxidil offer adjunctive approaches for the management of symptoms of acne and alopecia, respectively. Limited data suggest a relevance of vitamin D deficiency in the pathophysiology of PCOS (5), and therapeutic efficacy of vitamin D supplementation in the management of PCOS is being suggested (6).
To summarize, PCOS is a common disorder with a finite spectrum of manifestations; the diagnosis holds implications that extend well beyond the spectrum of presenting symptoms. Management strategies for PCOS should target not just the evident presenting complaint, but also the covert health burdens the individual patient is deemed at risk for. Beyond symptom control, management considerations must address endometrial protection, lifestyle modification to achieve target weight goals, and risk reduction strategies to minimize the future burden of CVD and type II diabetes. Pregnancy-related risks are not trivial, and implications for trans-generational burden are sobering; optimization of lifestyle parameters and weight reduction for the overweight and obese must be considered as the first-line fertility management strategy.

REFERENCES


Ovarian Cancer Stem Cells as the Source of Recurrence and Metastasis

INTRODUCTION

One of the major burdens in the treatment of epithelial ovarian cancer (EOC) is the high percentage of recurrence characterized by chemoresistance. The biology underlying the tumor’s high capacity of recurrence has not been elucidated. New data suggest that the cancer cell population is heterogeneous and contains a small subset of cells, the cancer stem cells (CSCs), which consist of a reservoir of cells that can self-renew and therefore maintain the tumor. These CSCs can divide and expand their pool as well as differentiate into non-CSCs, which constitute the bulk of the tumor. Unlike the CSCs, the non-CSCs are rapidly dividing and are therefore sensitive to therapies, which target highly proliferative cells. In the present study we identified, characterized and cloned the CSCs of EOC.

METHODS

EOC cells were isolated from malignant ovarian cancer ascites and solid tumors. Marker expression was determined using flow cytometry, western blots and immunocytochemistry. A xenograft nude mice model was used to establish tumor growth by injecting cancer cells either s.c. or i.p. Isolation of CD44+ population was done by FACS. All CSCs were maintained in spheroid cultures and monolayers.

RESULTS

The CSCs were identified in EOC cells isolated from ascites and solid tumors with the following characteristics: 1) cellular markers: CD44+, TLR4/MyD88+, IKKβ+ constitutive NF-κB activity and cytokine and chemokine production, chemoresistance to conventional chemotherapies, resistance to TNFα-mediated apoptosis, capacity to form spheroids in suspension, and a unique microRNA phenotype; 2) tumor formation in animals: 100% CD44+ cells formed tumors that contained 10% CD44+ and 90% CD44-negative cells. Re-injection of isolated CD44+ cells from previous engraftments was able to again recapitulate the original tumor phenotype. Isolation and in vitro treatment of CD44+ cells from fresh samples showed resistance to carboplatin and paclitaxel. In contrast, the sorted CD44-negative cell population from the same sample/patient was chemosensitive.

CONCLUSION

We report for the first time the cloning of ovarian cancer stem cells and their molecular characterization. Present chemotherapy modalities transiently eliminate the bulk of a tumor but leave a core of cancer cells with a high capacity for repair and renewal. The CSC corresponds to the core of malignant cells that promotes recurrence and chemoresistance. These clones represent a unique tool that may be used for the development of new therapies targeting this cell population and for a better understanding of recurrence.

PUBLICATION

Surgical Approaches to Apical Vault Suspension

INTRODUCTION

Pelvic organ prolapse is a hernia or defect of the support structures of the vagina that results in a bulge or protrusion of the female pelvic organs. The vagina can be divided into three compartments: anterior, posterior and apical. The resulting vaginal hernias or pelvic organ prolapse can be in any one, two or all three compartments. Pelvic organ prolapse includes anterior vaginal wall prolapse (cystocele), posterior vaginal wall prolapse (rectocele), uterine prolapse and vaginal vault prolapse after hysterectomy. Pelvic organ prolapse is a common, life-altering disease with 2.9% of community dwelling women in the United States experiencing severe symptoms (1).

Women with pelvic organ prolapse have the option of different treatment plans. These are based on a woman’s symptoms and preferences. These treatment options include expectant management, pelvic floor muscle exercises, pessary use or surgery. In the United States, a woman’s lifetime risk of undergoing surgery for pelvic organ prolapse or other pelvic floor disorders by the age of 80 is 11.1% (2). About 200,000 inpatient surgical procedures and 45,000 ambulatory surgical procedures for the correction of pelvic organ prolapse are performed annually (3-5).

THE OBJECTIVES OF THIS DISCUSSION ARE:

1) To review relevant anatomy related to pelvic support.
2) To describe different methods for surgical apical correction, including oblitative, restorative, compensatory and augmentation procedures.

ANATOMY RELATED TO PELVIC SUPPORT

Normal pelvic support is provided by a combination of connective supportive tissue and pelvic floor muscles. DeLancey first described the three levels of pelvic organ support in 1992 (6). Level I support is the support of the apical vagina and uterine cervix. Level II support is the support of the lateral vaginal walls. Level III support is the support of the perineal body, the outlet of the vagina. Level I (apical) support is comprised of two structures: 1) the cardinal ligaments traversing from the uterine cervix to the pelvic side walls and 2) the uterosacral ligaments traversing from the level of the external os of the uterine cervix to the pelvic side walls. Level II (lateral) support comes from the insertion of the vaginal tissue into the arcus tendineus fascia lata (ATFL) in the anterior vagina, also called the white line, which traverses from the ischial spine to the pubic symphysis. On the posterior wall, lateral vaginal support is provided by the arcus tendineus rectovaginalis. Level III (vaginal outlet) support comes from the intact perineal body, also called the central tendon of the perineum. The perineal body is the confluence of four separate muscle insertions: 1) the bulbocavernosus muscle, 2) the superficial transverse perineal muscle, 3) the deep transverse perineal muscle, and 4) the external anal sphincter. In posterior prolapse, the perineal body is often detached from the rectovaginal septum. Reattaching the perineal body to the rectovaginal septum can restore posterior vaginal support and correct perineal descent.
Anterior vaginal wall prolapse (cystocele) was demonstrated to correlate to apical prolapse (either the external os of the cervix or the top of the vaginal vault) (7). Therefore, evaluation of apical support is necessary prior to any surgery to address pelvic organ prolapse.

**SURGICAL METHODS OF APICAL SUPPORT**

The surgical approach to apical vault support can be divided into four main categories: oblitative procedures, restorative procedures, compensatory procedures and augmentation procedures.

**OBLITERATIVE PROCEDURES**

Obliterative procedures for the correction of apical pelvic organ prolapse involve the removing of vaginal mucosa to close the vagina. The two main oblitative procedures include: 1) the modified LeFort partial colpocleisis, where the uterus is left in situ and two side channels are created to allow for drainage from the cervix/uterus, and 2) the total colpectomy and colpocleisis, a procedure performed after hysterectomy (concurrent or remote), removing all vaginal mucosa and closing the vagina. The Pelvic Floor Disorders Network (PFDN) prospectively followed 152 women with a mean age of 79 years (± 6) undergoing oblitative vaginal procedures (8). The PFDN noted significant improvement in disease specific quality of life and prolapse symptoms with 95% of women “Satisfied” or “Very Satisfied” after the procedures. Postoperative regret after the oblitative vaginal procedure, which removes a woman’s ability for vaginal coitus, has been reported between 0% and 13%. No significant risk factors for postoperative regret have been demonstrated, and neither a current partner nor age is predictive of regret (9, 10).

Complications after oblitative procedures are low. Sung et al. reported low mortality and postoperative complications of oblitative procedures, even in patients over the age of 80 years (11). Uterine and cervical cancers have been reported after modified LeFort procedures, leading some experts to advocate endometrial biopsy prior to the time of the LeFort procedure as well as office endometrial biopsy prior to procedure (12). Surgeons should balance the need for sampling the endometrium with the risks of this sampling. De novo rectal prolapse after oblitative vaginal procedures has also been reported. Early studies have not been able to quantify the rate of de novo rectal prolapse after these oblitative vaginal procedures (13).

**RESTORATIVE PROCEDURES**

**UTEROSACRAL LIGAMENT SUSPENSION (USLS)**

As noted above, the apical support for the uterus is comprised of two structures: 1) the cardinal ligaments traversing from the uterine cervix to the pelvic side walls and 2) the uterosacral ligaments traversing from the level of the external os of the uterine cervix to the pelvic side walls. Uterine prolapse occurs due to tears or attenuation of the uterosacral ligaments leading to elongation and lack of support. Restorative procedures for apical prolapse involve the reattachment of the vaginal cuff to the shortened or proximal uterosacral ligaments above the area of attenuation and weakness. Often this reattachment or shortening is done at the level of the ischial spine to provide support as well as to avoid the ureter. At the level of the cervix, the ureter is 0.9 (±0.4) cm lateral to the uterosacral ligament; however, at the level of the ischial spine, the ureter is 2.3 (± 0.9) cm lateral (14).

The USLS is a vaginal procedure to reattach the uterosacral ligaments to the vaginal cuff. The two major approaches to reattaching the uterosacral ligaments to the vaginal cuff at the time of vaginal hysterectomy to address apical prolapse are: 1) the modified McCall’s culdoplasty and 2) the high ipsilateral uterosacral ligament suspension first described by Shull et al (15). Karram et al. reported outcomes after high ipsilateral uterosacral liga- ment suspension in 168 women (16). Recurrent prolapse was noted in 6.5% of women within the first two years after surgery. In a follow-up report 3.5 to 7.5 years after surgery, 15.3% of women experienced recurrent symptomatic pelvic organ prolapse (17). These reports demonstrate the consistent finding that the single most important risk
factor for recurrent pelvic organ prolapse after surgical correction is time. Complications of the vaginal uterosacral ligament suspension include: 1) ureteral compromise of 4% to 11% and 2) sensory nerve pain reported in up to 3.8% (7/182) of women with resolution between six weeks and six months (18-20).

Laparoscopic uterosacral ligament suspension is a newer technique to address apical pelvic organ prolapse as a restorative procedure (20). Theoretically, benefits of the laparoscopic approach to uterosacral ligament suspension are: 1) improved visualization of the ureter and rectum during suture placement, 2) enhanced anatomic dissection for identification of uterosacral ligaments, and 3) using the laparoscopic approach to facilitate other laparoscopic repairs.

**COMPENSATORY PROCEDURES**

**Sacrospinous Ligament Fixation (SSLF)**

The sacrospinous ligament (SSL) runs between the ischial spine and the lower portion of the sacrum. The SSL is a cord-like structure that lies within the body of the coccygeus muscle. The pudendal neurovascular bundle lies directly posterior to the ischial spine, traveling through Alcock’s canal. In addition, the inferior gluteal vessels course behind the SSL midway between the ischial spine and the sacrum (21). Neither the uterus nor the apex of the vagina is naturally attached to the SSL; however, the SSL is utilized to compensate for the failure of apical support structures of the vagina by fixating the vaginal apex to the SSL with sutures.

In a systematic review of the sacrospinous ligament fixation procedure, Morgan et al. reported on 979 women from 17 published cohorts (22). Inclusion criteria for this systematic review require follow-up at least 12 months after surgery and the objective measurement of postoperative support by either the Baden-Walker grading system or the Pelvic Organ Prolapse Quantification system. In this review, failure was considered Baden-Walker Grade 2 or greater, meaning failure was a recurrence to the level of the vaginal hymen in any compartment (anterior, posterior or apical). Failure at any site was 28.8% (95% Confidence Interval [CI] 22.5%, 35.1%). Failure in the anterior, apical and posterior compartments was 21.3% (95% CI 17.3%, 25.3%), 7.2% (95% CI 4.0%, 25.3%) and 6.3% (95% CI 4.2%, 8.4%), respectively.

Classically, the major criticism of the SSLF procedure is the overstretching of the anterior vaginal wall. This is due to the fact that the SSLF is a compensatory procedure that attaches the vaginal vault to a structure to which it is not anatomically attached. Cadaveric studies have demonstrated that the attachment of the vaginal vault to the SSLF results in a downward deviation of 28° to 32° and a lateral deviation of 22° of the vaginal axis. The Morgan systematic review does counter this argument with anterior wall failures of 21% (22). Another critique of the SSLF is de novo dyspareunia as a result of the deviation of the vaginal axis. Actual rates of postoperative and de novo dyspareunia are unclear, as sexual function after any procedure for pelvic organ prolapse has not been systematically studied.

Currently, there are no published randomized controlled trials (RCT) of the two main vaginal procedures for the correction of apical vaginal prolapse, the USLS vs. the SSLF. The PFDN has finished recruitment for the Operations and Pelvic Muscle Training in the Management of Apical Support Loss: The OPTIMAL Trial (23). This multi-center RCT investigates the USLS vs. the SSLF, and two-year results are expected to be reported soon.

**AUGMENTATION PROCEDURES**

**Abdominal Sacrocolpopexy (ASC)**

The Abdominal Sacrocolpopexy (ASC) procedure was first described in 1962 by Lane as a technique to address recurrent enterocele by placing a graft between the vaginal apex and affixing this graft to the anterior longitudinal ligament of the sacrum. The ASC procedure requires the surgeon to have an expert understanding of the anatomy of the presacral space. Important anatomy for the surgeon to identify for the presacral dissection includes: 1) the sacral promontory, 2) the aortic bifurcation, 3) the right ureter, 4) the medial edge
of the sigmoid colon, 5) the common iliac vessels and 6) the middle sacral vessels.

In 1994, the PFDN published a systematic review of the ASC procedure and emphasized key points in surgical technique: 1) to use a graft or mesh material to intervene the distance between the vaginal apex and the anterior longitudinal ligament of the sacrum; 2) to avoid excess tension on the anterior vaginal wall predisposing women to postoperative stress urinary incontinence; 3) to fix the graft/mesh material to the anterior longitudinal ligament of the sacrum around the sacral promontory (S1 or S2) to decrease the risk of life-threatening hemorrhage of the middle sacral vessels at the level of S3 or S4; 4) to avoid placing permanent graft material on a denuded vaginal apex to decrease the risk of mesh complications, and 5) to place multiple sutures to attach the mesh/graft material to the vaginal apex as failures from the ASC most often result from the mesh/graft pulling off the vagina rather than failures at the anterior longitudinal ligament (24).

Many mesh and graft materials have been used in the ASC procedure. In 2006, Culligan et al. published the results of an RCT investigating the use of type I macroporous monofilament polypropylene mesh (n=54) vs. cadaveric fascia lata (n=46) (25, 26). At 12-month and 60-month follow-ups, failures (recurrent symptomatic pelvic organ prolapse) were significantly higher in the cadaveric fascia lata group vs. the polypropylene mesh (12-month, 37% vs. 9%, p = .007) (60-month, 38% vs. 7%, p = .02).

The use of permanent mesh material to augment surgical repairs for pelvic organ prolapse is balanced by the risk of complications of rejection, erosion and infection of the permanent mesh material. Increased risk of vaginal mesh erosion has been reported in ASC procedures with concomitant total abdominal hysterectomy (27, 28). Bensinger et al. reported that supracervical hysterectomy was able to provide equivalent pelvic support without increasing the prevalence of postoperative vaginal mesh erosion (29).

The Colpopexy and Urinary Reduction Efforts (CARE) trial was an NIH-funded, multi-center RCT conducted by the PFDN (30). The CARE trial recruited 322 stress continent women with Stage II or greater pelvic organ prolapse undergoing ASC for surgical correction of prolapse. The objective of the CARE trial was to determine if a prophylactic anti-incontinence procedure, namely a retropubic urethropexy or Burch procedure, at the time of ASC was beneficial in stress continent women. The advantage of the CARE trial is superior data collection of postoperative outcomes and complications with standardized and reproducible measurements. Two-year failure rates of the ASC were reported as objective Stage II prolapse or greater—43.2% (108/250); however, Stage III prolapse or greater only occurred in 2.0% of women (5/250), and re-operation for recurrent symptomatic prolapse was 2.6% (8/311). Serious adverse events (SAEs) from ASC included prolonged initial hospitalization of 1.2% (4/322), 30-day hospital readmission for bowel symptoms of 3.4% (11/322), hospitalization for ileus or small bowel obstruction over two years of 6.7% (21/311), mesh or suture erosion of 6.4% (20/311), and wound complications of 3.2% (10/311) (31, 32).

Three RCTs of ASC vs. SSLF have been published (33-35). In the recent Cochrane Review of these three trials, Maher et al. concluded that ASC was better than SSLF in terms of a lower rate of recurrent vault prolapse (RR 0.23, 95% CI 0.07 to 0.77) and less dyspareunia (RR 0.39, 95% CI 0.18 to 0.86). Disadvantages of ASC include a large abdominal incision, increased morbidity from laparotomy vs. vaginal procedures, and a longer hospital stay.

**MINIMALLY INVASIVE SACROCOLPOPEXY**

Minimally invasive sacrocolpopexy procedures have recently been offered to women with apical prolapse to provide the advantages of the traditional open procedure with a faster recovery and less pain.

**LAPAROSCOPIC SACROCOLPOPEXY (LSC)**

One RCT of LSC vs. ASC has been published by Paraiso et al (36). No statistically significant difference in surgical success between the LSC
and ASC was demonstrated. Women undergoing the LSC had longer operating times (269 min (±65) vs. 218 min (±60) (p<.0001), but shorter hospital stays (1.8 (days) (±1.0) vs. 4.0 (days) (±1.8) (p<.0001)). Theoretically, advantages of the LSC procedure include improved visualization of anatomic structures (Level III evidence), a shorter hospital stay (Level II-2 evidence) and decreased postoperative pain (Level III evidence). LSC disadvantages include a steep learning curve, increased operating room time and increased cost of disposable instruments.

**ROBOT ASSISTED LAPAROSCOPIC SACROCOLOPEXY (RSC)**

RSC advantages include a three-dimensional vision system, wristed instruments for full articulation and ergonomic positioning for the surgeon. Gellar et al. have published one comparative trial on short-term outcomes of RSC vs. ASC with a mean follow-up at six weeks (37). RSC had significantly decreased estimated blood loss (103 ml (±96) vs. 255 (±155), (p <.001)) and decreased hospital length of stay (1.3 days (± 0.8) vs. 2.7 days (±1.4), (p <.001)). Disadvantages of the RSC procedure include increased operating times, loss of tactile feedback, a steep learning curve of the operating room staff and the surgeon (38) and increased use of semi-disposable instruments.

**CONCLUSION**

Many surgical techniques to address apical vault prolapse exist. Currently, selecting a surgical approach to apical prolapse surgery is a balance of patient characteristics and patient goals. More adequately powered RCTs are urgently needed to determine vital questions in prolapse surgery including surgical approach, surgical technique and symptom relief after surgery.
REFERENCES


OBJECTIVE

Nuchal translucency (NT) is an integral component of the first trimester screen for trisomy 21 and trisomy 18 that is routinely offered to pregnant women with singleton or twin pregnancies in the first trimester. Increasing NT measurements are associated with increasing risks for aneuploidy. Beyond this, increased NT thickness has been associated with adverse outcomes including birth defects and fetal loss. Twin pregnancies are at increased risk for a multitude of adverse obstetrical and neonatal outcomes such as suboptimal fetal growth, preterm birth and perinatal loss. As such, identifying a subgroup of twin pregnancies requiring intensive monitoring and evaluation would be a worthwhile goal. In monochorionic twins, inter-twin nuchal translucency discordance has been investigated, and some suggest discordance identifies a population of twins at particularly high risk for developing twin-to-twin transfusion syndrome (TTTS) and other adverse fetal outcomes. Currently, no study to date has investigated the significance of NT discordance in a cohort of all twin pregnancies (including dichorionic twins) that are seen for routine first trimester aneuploidy. The current study was designed to identify and potentially estimate an association between NT discordance and common adverse perinatal outcomes in chromosomally normal twin fetuses with normal NT values (<3mm).

METHODS

In this retrospective cohort study, all twin pregnancies with ultrasounds performed between 11 0/7 and 13 6/7 weeks in the years 2004-2009 at Yale New Haven Hospital (YNHH) were identified using an established database. Inclusion criteria were twin pregnancies with two fetal heartbeats on ultrasound, a crown rump length measuring 45 mm to 84 mm, delivery at YNHH, chromosomally normal fetuses, and an NT thickness less than 3 mm. NT discordance was calculated as the difference between two fetuses expressed as a percentage of the larger twin \((\text{NT}_1 - \text{NT}_2 \div \text{NT}_1 \times 100)\). NT discordance was defined as discordance equal to or greater than 30%. The primary outcome was a composite of obstetrical (fetal demise, preterm birth <32 weeks) and neonatal adverse outcomes (Apgar <7 at 5 minutes, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis and neonatal demise in at least one twin). Statistical analysis used t-test, chi-square, Wilcoxon test and multivariable logistic regression modeling (p<0.05 defined statistical significance).

RESULTS

There were 304 twin pairs that met the inclusion criteria. Of these, 262 were dichorionic and 63 (20.7%) of all twin pregnancies were identified to have discordant NT equal to or greater than 30%. There was no difference in the composite perinatal outcome between twins with discordant and non-discordant NT measurements (19.1% vs. 29.1%, respectively, p = 0.11). However, in planned secondary analysis, twins with discordant NT were more likely to be small for gestational age compared with non-discordant NT twins (57.1% vs. 36.1%; p = 0.002; OR 2.36 [95% CI, 1.34-4.15]). This association persisted after multivariate logistic regression, adjusting for maternal age, parity, race, maternal disease, gestational age at NT measurement, chorionicity, use of assisted reproduction, tobacco use and preterm birth (OR 2.64 [95% CI, 1.43-4.82]).
CONCLUSIONS

Chromosomally normal twin pregnancies with discordant nuchal translucencies within the normal range are more likely to produce at least one neonate that is small for gestational age compared with non-discordant NT pregnancies. However, other outcomes, such as preterm delivery and perinatal and neonatal morbidity and mortality, do not differ. While this finding is overall reassuring for the 20% of twin pregnancies that present with NT discordance ≥30%, heightened antepartum fetal surveillance of fetal growth may be warranted.
OBJECTIVE

Tryptophan 2,3-dioxygenase (TDO) is expressed in the endometrium and catabolizes tryptophan, a precursor in the biosynthesis of serotonin. Tryptophan metabolism is an important mechanism for regulation of serotonin levels. Catabolism of tryptophan is also critical to suppress immune rejection of embryos during implantation. Preimplantation mouse embryos are known to express serotonin receptors, specifically the 5-HT1D and 5-HT7 serotonin receptor sub-types. Here we demonstrate that HOXA10 regulates endometrial TDO expression and improves embryo viability through increased serotonin production and local immune suppression.

METHODS

Pregnant mice were treated with intrauterine transfection of pcDNA-HOXA10 plasmid or control (empty plasmid). Uteri were dissected and RNA extraction and immunohistochemistry. RNA was isolated for RT-PCR analysis. Quantitative RT-PCR (qRT-PCR) was performed to quantify expression of tryptophan 2,3-dioxygenase. Immunohistochemistry was performed to localize serotonin within the endometrium. Ishikawa cells, human endometrial stem cells and third trimester decidual cells were also transfected with pcDNA-HOXA10 plasmid or control (empty plasmid). RNA was again extracted and TDO expression was quantified by qRT-PCR. Pregnant mice were treated with intrauterine transfection of pcDNA-HOXA10 antisense or control. Embryos were flushed 48 hours later for analysis. A separate cohort of pregnant mice was treated with intrauterine injection of serotonin receptor antagonists or control. Embryos were also collected from these mice 48 hours later for analysis. Female mice were also mated with vasectomized males and then treated with intrauterine injection of pcDNA-TDO plasmid or control. Sesame oil was then injected to induce a decidual reaction. Uteri were later dissected and immunohistochemistry was performed for CD3 (an antigen present on mature T-cells). Quantitative PCR and CD3+ staining results were compared using student t-test. Embryo quality (reflected as percent blastocysts) results were compared using independent samples t-test. P<0.05 was considered statistically significant.

RESULTS

Transfection of pcDNA-HOXA10 to the murine uterus increased uterine TDO expression. In vitro, epithelial cell TDO expression was decreased after transfection with HOXA10. Decreased glandular TDO in response to HOXA10 may augment serotonin production by increasing tryptophan availability. Conversely, stromal TDO expression increased with constitutive HOXA10 expression. In mice, epithelial serotonin was increased in response to constitutive expression of HOXA10. Embryo quality was impaired after treatment with HOXA10 antisense. Blockade of serotonin receptors 1D and 7 also resulted in impaired embryo development, indicating an essential role for HOXA10 induction of TDO and subsequent serotonin production in embryo development. Transfection of pcDNA-TDO decreased the number of CD3+ T-cells in the endometrial stroma during decidualization.

CONCLUSIONS

We have shown a novel mechanism by which HOXA10 differentially regulates endometrial TDO expression. In the endometrial stroma, HOXA10 increases TDO mRNA, which may increase tryptophan catabolism, allowing for immune tolerance at the time of embryo implantation. In endometrial glands, HOXA10 decreases TDO mRNA, leading to increased serotonin that in turn acts to promote normal embryo development.
Preimplantation Factor Promotes First Trimester Trophoblast Invasion

Christina M. Duzyj, MD, MPH; Eytan R. Barnea, MD; Min Li, PhD; Se-Tese Joseph Huang, MD, PhD; Graciela Krikun, PhD; Michael J. Paidas, MD

1 Yale Women and Children’s Center for Blood Disorders, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

2 SIEP, Society for the Investigation of Early Pregnancy, Cherry Hill, New Jersey

3 Department of Obstetrics, Gynecology and Reproduction, UMDNJ - Robert Wood Johnson Medical School, Camden, New Jersey

4 Reproductive Biology Unit, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

OBJECTIVES

Preimplantation factor (PIF) is a novel embryo-derived peptide that influences key processes in early pregnancy, including immunity, adhesion, remodeling and apoptosis. We explored the effects of synthetic PIF (sPIF) on trophoblast invasion.

METHODS

Invasion patterns of immortalized cultured HTR-8 trophoblast cells were analyzed through Matrigel extracellular matrix +/- sPIF (25-100nM) in a transwell assay. Effects were compared with epidermal growth factor (EGF) 10μg/mL and scrambled amino acid sequence of PIF or media alone as controls.

RESULTS

sPIF enhances trophoblast invasion at physiologic doses [at 50nM 260% (174%-346%, 95% CI, p=0.05); 100nM 178% (170%-184%, p<0.02)]. EGF added to sPIF does not enhance trophoblast invasion as obtained by sPIF alone [sPIF 50nM+EGF, 238% (237%-239%, p<0.02); sPIF 100nM+EGF 269% (265%-273%, p<0.04)]. Scrambled PIF’s effects were not significant.

CONCLUSION

sPIF promotes trophoblast invasion in vitro. Trials to evaluate PIF’s efficacy to treat and prevent conditions associated with inadequate trophoblast invasion appear clinically important.
Management of Ureteral Obstruction in Gynecologic Malignancies

Sara Isani, MD; John Colberg, MD; Peter Schwartz, MD
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

BACKGROUND

Ureteral obstruction is a common problem faced by patients who have gynecological malignancies, but there is no consistent approach to its management.

METHODS

We carried out a retrospective case series of all gynecologic oncology patients with ureteral obstruction who underwent either ureteral surgery or ureteral stent placement from 2000 through 2009 at our institution (n=53). We reviewed charts through April 2010 to determine the frequency of characteristics associated with ureteral obstruction as well as outcome data based on the type of urologic intervention performed.

RESULTS

Cancers included 22 cases of the ovary, 15 of the cervix, 10 of the uterine corpus and 6 others. Twenty-one patients underwent ureteral surgeries such as ureteroureterostomy, ureteroneocystostomy and diverting conduit, most often in the setting of secondary cytoreduction; 32 had ureteral stent placement. The mean post-procedure follow-up period was 19.8 months. Of the patients who had at least three months of follow-up, procedure failure caused need for additional intervention, such as repeat surgery, stent or percutaneous nephrostomy tube placement, in 8 of 21 patients in the surgery group and 12 of 23 patients in the stent group ($\chi^2=0.40$, p=0.56); the overall need for further ureteral interventions was 10 of 21 and 21 of 23, respectively ($\chi^2=8.07$, p=0.004). Of the patients for whom survival data was known during the review period, 6 out of 14 died in the surgery group, and 23 out of 28 died in the stent group ($\chi^2=5.02$, p=0.02).

CONCLUSION

Ureteral obstruction is a complicated problem in certain patients with gynecologic malignancy, as evidenced by the fact that almost half of the patients in both our groups required extra procedures secondary to inadequate relief of obstruction, and the vast majority needed some additional intervention. The likelihood of death during the review period was significantly higher in the stent group than in the surgery group. This finding, however, was most likely related to disease burden rather than superiority of intervention.
Gestational Diabetes Screening: A Decision Analysis

Michael Reel, MD, MBA; Stephen Thung, MD
Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

OBJECTIVE

Gestational diabetes mellitus (GDM), carbohydrate intolerance manifesting or first recognized during pregnancy, is currently evaluated in the U.S. by a two-step testing process. An initial one-hour 50-gram glucose challenge test (GCT) is used as a screening test. If a patient screens positive, a definitive diagnosis of GDM is made by assessing performance on a three-hour 100g glucose tolerance test (GTT). There is no current consensus on the threshold used on the GCT to prompt GTT evaluation. The ACOG practice bulletin on GDM maintains that 130 or 140 mg/dL may be used as an appropriate screening threshold to indicate further testing (1). Even within our own institution, there are discordant practice patterns concerning the optimal GCT threshold.

There are maternal and fetal health consequences of GDM, including increased incidence of maternal hypertensive disease, fetal macrosomia, shoulder dystocia and birth trauma, although these relationships are complex and require careful control of highly correlated confounding variables such as weight, parity and race. Two recent prospective randomized controlled trials have provided high-quality data on the results of treatment of GDM (2, 3), and the results were incorporated into a recent systematic meta-analysis (4). The goal of this study is to formulate a decision analysis model incorporating costs of diagnosis, treatment and complications, probabilities of diagnosis and complications, and utilities of neonatal outcomes in order to comprehensively evaluate the cost-benefit relationship to society of using differing thresholds for screening for GDM.

METHODS

We created a decision analysis model to evaluate the results of pregnancies evaluated with a GCT screening at the end of the second trimester. Population prevalence of gestational diabetes and sensitivities and specificities of the GCT at thresholds of either 130 mg/dL or 140 mg/dL were used to simulate a cohort conditionally evaluated with a subsequent three-hour GTT, which is considered the gold standard for diagnosis of gestational diabetes. The analysis was from a societal perspective. Women diagnosed with GDM were assigned to diet or insulin therapy according to published rates of A1 and A2 diabetes. Costs of diagnosis, treatment including medication, diabetes testing supplies and meters, nutritional counseling, additional physician visits, surveillance ultrasound and additional NST testing were accumulated depending on diabetes diagnosis. The differential likelihood of preeclampsia, cesarean delivery, peripartum fetal death, shoulder dystocia and transient and permanent brachial plexus palsy was assessed, depending on the patient's status as a non-diabetic, treated or untreated gestational diabetic. Discounted utility values were assigned for outcomes, permitting quality adjusted life year (QALY) measurements. For all data points, baseline values and upper and lower values for sensitivity analysis were assigned. Testing characteristics and outcome probabilities were derived from published literature, with preference given to values derived from randomized controlled trials both individually and in structured meta-analyses. Cost information was derived from published literature and Medicare reimbursement tables, and adjusted by the medical component of the consumer price index to 2009 values. When an appropriate published value was not available, estimates were used based on available data. Marginal cost per quality adjusted life year gained was computed for each screening threshold. A value less than $100,000 is considered cost-effective.
RESULTS

Using baseline values for testing characteristics, GDM prevalence, costs, probabilities and utilities, a screening threshold of 130mg/dL produces an expected cost of pregnancy which is $10.20 more expensive than using a cutoff of 140mg/dL, and the marginal cost per QALY gained via this strategy is $364,758. The absolute number of fetal deaths and permanent brachial plexus palsies prevented per 1,000,000 pregnancies by using the more stringent screening threshold of 130mg/dL is 0.4 and 3.6, respectively. The cost to prevent one fetal death is $21,564,482 and to prevent one permanent brachial plexus palsy is $2,859,022. The model is most sensitive to changes in the probability of nerve palsy following shoulder dystocia. The reported incidence of palsy has a wide (10-fold) estimation in the literature, ranging from 4%-40%, leading to a range in QALY from $576,000 at 40% to $133,000 at 4%. The cost of a GTT produces QALY variation from $251,000 to $591,000, at GTT costs from $31.30 to $125.21. The QALY cost ranges from $133,000 to $522,000 by varying the probability and additional cost of care for preeclampsia, the probability and cost of brachial plexus palsy and the probability of fetal death over their assumed ranges. The QALY ranges from $179,000 to $4.3MM by varying the prevalence of GDM and the sensitivity and specificity of the 50-gram glucose screening test.

REFERENCES


CONCLUSION

Gestational diabetes carries increased morbidity relative to normal glucose tolerance; however, given the current costs of testing and treatment, the magnitude of benefit from treatment and the probability, cost and morbidity of complications of gestational diabetes, a glucose screening threshold of 130mg/dL is not cost-effective, relative to a threshold of 140mg/dL.
Uterine Serous Papillary Carcinomas Overexpress Human Trophoblast-Cell-Surface Marker (Trop-2) and Are Highly Sensitive to Immunotherapy with hRS7, a Humanized Monoclonal Anti-Trop-2 Antibody

Emiliano Cocco, MD1; Joyce Varughese, MD1; Christine E. Richter, MD1; Francesca Casagrande, MD1; Stefania Bellone, MD1; Karim El-Sabwi, MD1; Marta Bellone, MD1; Paola Todeschini, MD2; Dan-Arin Silasi, MD1; Masoud Azodi, MD1; Peter E. Schwarz, MD1; Thomas J. Rutherford, MD1; Sergio Pecorelli, MD2; Alessandro D. Santin, MD1
1Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut
2Division of Gynecologic Oncology, University of Brescia, Brescia, Italy

PURPOSE

To evaluate the expression of human trophoblast cell-surface marker (Trop-2) and the potential of hRS7, a humanized monoclonal anti-Trop-2 antibody, as a novel therapeutic strategy against uterine serous papillary carcinoma (USPC), a biologically aggressive and chemotherapy-resistant variant of endometrial cancer.

METHODS

Trop-2 expression was evaluated by real-time-PCR and flow cytometry in six primary uterine serous papillary carcinoma cell lines. Sensitivity to hRS7 antibody-dependent-cellular-cytotoxicity (ADCC) was tested in standard 5-hrs ⁵¹Cr release-assays against primary USPC cell lines expressing different levels of Trop-2.

RESULTS

Trop-2 mRNA transcript was significantly overexpressed in three out of six USPC primary cell lines when compared to normal human endometrial cells (NEC) [p=0.005]. Consistent with RT-PCR data, high surface expression of Trop-2 was detected by flow cytometry in Trop-2 overexpressing cell lines [i.e., percentage of positive cells = 100% in all three positive cell lines, median (minimum-maximum) MFI (mean fluorescence intensity) of 184.2 (62.5-276.2)]. Importantly, while these USPC cell lines were found highly resistant to natural killer-dependent cytotoxicity in the absence of the hRS7 antibody (range of killing 1.1% to 12.4%), they showed high sensitivity to hRS7-mediated ADCC in vitro (range of killing 28.2% to 64.4%) (p< 0.001).

CONCLUSION

Primary USPC cell lines may overexpress Trop-2 at mRNA and protein level and are highly sensitive to hRS7-mediated cytotoxicity in vitro. hRS7 may represent a novel, potentially highly effective therapeutic strategy in patients harboring advanced, recurrent or metastatic USPC refractory to standard treatment modalities.
ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the Society for Maternal-Fetal Medicine 31st Annual Meeting, February 7-12, 2011, San Francisco, California

ORAL PRESENTATIONS

Calcifying Nanoparticles (NP) as Novel Etiologic Agents of Idiopathic Preterm Birth (iPTB) and Preterm Premature Rupture of the Membranes (PPROM). L. Shook, C.S. Buhimschi, A.T. Dulay, G. Zhao, U.A. Ali, C. Han, K. Campbell, E. Werner, I.A. Buhimschi.


*The work received the 2011 SMFM Research Excellence Award.


POSTER PRESENTATIONS


Preimplantation Factors’ Effect on Decidua: Signaling Pathways Suggest Correlation with Neurological Development and Diseases. C. Duzyj, E. Barnea, L. Jebailey, J. Annunziato, M. Romano, G. Krikun, S.J. Huang, M. Paidas.

Molecular Assessment of the Myometrium During Preterm (PTL) and Term Labor (TL) Using Gene Expression and Biological Pathway Analysis. C. Mason, C.S. Buhimschi, I.A. Buhimschi, C.P. Weiner.
Screening for Gestational Diabetes with a One-Hour Glucose Challenge Test: Is a 130mg/dL Threshold More Cost-Effective Than a 140mg/dL Threshold? M. Reel, E. Werner, C.M. Pettker, E.F. Funai, S.F. Thung.


A Functional Role for TLR4 Adaptor Protein, Soluble Myeloid Differentiation Factor (sMD)-2, in Modulating the Fetal Inflammatory Response in Infection Induced Preterm Birth (PTB). A.T. Dulay, C.S. Buhimschi, S.Y. Lee, S.S. Abdel-Razeq, G. Zhao, C. Han, L. Shook, I.A. Buhimschi.

ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral Presentations at the Society of Gynecologic Oncologists 42nd Annual Meeting, March 6-9, 2011, Orlando, Florida

ORAL PRESENTATIONS

Uterine Serous Papillary Carcinomas Overexpress Human Trophoblast Cell-Surface Marker (Trop-2) and Are Highly Sensitive to Immunotherapy with hRS7, a Humanized Anti-Trop-2 Monoclonal Antibody. J. Varughese.

Phase II Trial of Cetuximab in the Treatment of Persistent or Recurrent Squamous or Non-Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. A. Santin.
ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral Presentations at the American Urogynecologic Society 31st Annual Meeting, September 30-October 2, 2010, Long Beach, California

ORAL PRESENTATIONS


ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS


ORAL PRESENTATIONS


Effects of Bazedoxifene/Conjugated Estrogens on Metabolic Parameters: A Randomized, Placebo-Controlled Clinical Trial in Postmenopausal Women. H.S. Taylor, S. Mirkin, A. Chines.


POSTER PRESENTATIONS


Increased Expression of Uroplakins in Endometrium from Patients with Endometriosis. J. Luk, H. Taylor.

Aberrant HOXA10 Methylation in Patients with Asherman’s Syndrome and Uterine Septum: A Possible Contribution to Poor Reproductive Outcomes. J. Kulp, H. Taylor.


Optimal Time for ICSI after hCG Administration and Oocyte Incubation Period. I. Obeso, J. Roesles, G. Garcia, R.M.D. Santos, P.M.D. Galache, P. Patrizio.


Predictors of Spontaneous Reduction (SR) in Art Cycles. Y.E. Sükür, T. Altun, L. Pal.
ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the Society for Gynecologic Investigation 58th Annual Meeting, March 16-19, 2011, Miami Beach, Florida

ORAL PRESENTATIONS


Ischemia/Reperfusion Injury Promotes Migration of Bone Marrow-Derived Stem Cells to Endometrium. H. Du, H. Naqvi, H.S. Taylor.


POSTER PRESENTATIONS

Short Hairpin Mediated Knockdown of HOXA11 Leads to Increased Activation of Matrix Metalloproteinases, Decreased Expression of Collagen Subtypes and Altered Biomechanical Properties of the Uterosacral Ligament in Mice. K. Connell.


Aberrant HOXA10 Methylation in Patients with Uterine Myomas, a History of Endometriosis or Uterine Septum: A Possible Contribution to Poor Reproductive Outcomes. J.L. Kulp, H.S. Taylor.

Migration of Stromal Cells with Altered Steroidogenic Capacity from Endometriotic Lesions Selectively to the Uterus. X. Santamaria, E. Massasa, Y. Feng Y, H.S. Taylor.

Combination Treatment with Aspirin and Heparin Exacerbates the Antiphospholipid Antibody-Induced IL-8 Response in First Trimester Trophoblast. C. Han, M. Mulla, J. Brosens, L. Chamley, M. Paidas, V. Abrahams.


Interferon Gamma (INF) Receptors 1 and 2 Mediate INF-Enhanced Chemokine Expression in Human Decidual Cells. C.J. Lockwood, Y. Huang, L. Buchwalder, J. Huang, F. Schatz.


Pro-Inflammatory Cytokine-Stimulated First Trimester Decidual Cells Enhance Macrophage Induced Trophoblast Apoptosis. M. Li, Z. Wu, S.J. Huang.

Tissue Factor Expression in Ovarian Cancer: Implications for Immunotherapy with hI-con1, a Factor VII-IgGFc Chimeric Protein Targeting Tissue Factor. S. Bellone, E. Cocco, J. Varughese, N. Buza, K. Lin, M. Bellone, P. Todeschini, D. Silasi, M. Azodi, P.E. Schwartz, T.J. Rutherford, L. Carrara, R. Tassi, S. Pecorelli, C.J. Lockwood, A.D. Santin.


TLR Agonists Result in Differential Cytokine Expression by First Trimester vs. Term Basalis vs. Term Parietalis Human Decidual Cells. G. Krikun, G. Mor, V. Abrahams, F. Schatz, S. Guller, C.J. Lockwood.


Decreased Placental Levels of CCL5 are Associated With Neurodevelopmental Delay in Children. S.Guller, Z. Tang, T. Niven-Fairchild, J.E. Williams, V.M. Abrahams, G. Mor, R.A. Ehrenkranz.


Welcome to Our New Ob/Gyn Interns

We are pleased to announce the interns for 2010-2011. All six are outstanding and highly accomplished physicians.

**ASIMA AHMAD, MD, MPH – University of Chicago Division of the Biological Sciences – The Pritzker School of Medicine**

Asima received her BA (Economics, Biological Sciences) at the University of Chicago and her MPH (Public Health & Global Health) at Harvard School of Public Health. She did an internship with the Reproductive Health Department at World Health Organization in Geneva, Switzerland, gathering and analyzing data regarding maternal mortality in Mongolia. She has been involved in numerous volunteer programs, including the Geographic Medicine Scholars Program. She was one of eight scholars selected to spend a month in India observing and participating in medical care. Asima is fluent in Punjabi, Urdu and Hindi. Among her hobbies and interests she lists South Asian fashion design, gourmet cooking and South Asian dance.

**STEPHANIE BAKAYSA, MD, MPH – University of Vermont College of Medicine**

Stephanie received her BS (Biology) at Tufts University and her MPH (Public Health, Epidemiology) at Boston University School of Medicine. Her fourth-year research project at the University of Vermont FAHC Ob/Gyn department was on the use of buprenorphine in pregnancy, and was presented at the Annual Scientific Meeting of the Society for Maternal-Fetal Medicine. Stephanie was a healthcare volunteer in an earthquake region in Kashmir, assisting in the emergency room, on labor and delivery, and with maintenance projects in the field hospital. Her hobbies and interests include rugby, skiing and biking. She is conversant in Spanish.

**JONATHAN BLACK, MD, MPH – University of Rochester School of Medicine and Dentistry**

Jonathan received his BA (Economics) at the University of Rochester and his MPH (Public Health) at the University of Rochester School of Medicine and Dentistry. Among his research projects was a study looking at a mother’s perception of a child born with a cleft lip and/or palate. He designed and completed this study during a medical mission to Colombia aimed at repairing cleft lip/palate defects in children in underserved rural communities. These findings were recently published in the *Cleft Palate and Craniofacial Journal*. Jonathan has remained active in a number of similar community-based volunteer programs throughout medical school. His hobbies and interests include tennis, squash, photography and ultimate Frisbee.
MAI HOANG, MD – University of Vermont College of Medicine

Mai received her BS (Microbiology, Immunology & Molecular Genetics) at the University of California, Los Angeles, graduating cum laude. For her fourth-year MD research project, she spent several months in a basic science research lab studying the molecular mechanisms of preeclampsia. Specifically, she is using a rat model of gestational hypertension to look at the expression and localization of the two VEGF receptors (VEGFR-1 and VEGFR-2) in hypertensive and normotensive pregnancies. She was the recipient of the Frymoyer Global Health Scholarship to attend a clinical training course in Tropical Medicine and Infectious Disease in Lima, Peru. Over the years, Mai has been involved in a number of volunteer medical programs, including assisting in global health awareness events such as AIDS Awareness Week and in fundraising efforts to build a medical clinic in Ghana. Mai is fluent in Vietnamese and medical Spanish. Her hobbies and interests include singing, dancing and painting.

AMANDA ROSTKOWSKI, MD, PhD – Chicago Medical School at Rosalind Franklin University of Medicine and Science

Amanda received her BA (Biology, Chemistry) at the College of Notre Dame of Maryland. During her undergraduate career, she was elected AOA and received numerous academic and leadership awards. The focus of her PhD thesis at Chicago Medical School was to investigate the role of neuropeptide Y (NPY) and corticotrophin releasing factor (CRF) in the amygdala of rats, and she has several publications in highly respected scientific journals. Amanda has remained actively involved in her community, including leadership positions in several student organizations, and she served as a Student Dean at Chicago Medical School. The list of her interests and hobbies includes horseback riding (she is a riding instructor), singing and “cooking gourmet feasts.”

JANELLE WARMINGTON, MD – University of California, Los Angeles – David Geffen School of Medicine

Janelle received her BS (Biomedical Sciences) at the University of California, Riverside. She has been involved in a number of medical volunteer projects over the years, including a medical mission and education program in Costa Rica in which she worked closely with orphanages, hospitals and rural clinics to provide basic healthcare to the underserved population. She has been actively involved in the student-run healthcare clinics at both UCR and UCLA, providing basic healthcare services to the local homeless communities. Janelle’s hobbies and interests include traveling to Spanish-speaking countries, participating in running and cycling events, painting, and arts and crafts. She was team captain of intramural volleyball at UCR and led her team to an IM championship. She is fluent in medical Spanish.
Our 2010 Residency Program Graduates And Their Next Destinations

EVE BERNSTEIN
Maternal-Fetal Medicine Fellowship
University of Washington

SARA ISANI
Gynecologic Oncology Fellowship
Albert Einstein, NY

LEO DOHERTY
Reproductive Endocrinology & Infertility Fellowship
Yale University

MICHAEL REEL
Private Practice
Obstetrics, Gynecology & Menopause Physicians, YNHH

CHRISTINA DUZYJ
Maternal-Fetal Medicine Fellowship
Yale University

JOYCE VARUGHES
Gynecologic Oncology Fellowship
Yale University
Our 2011 Residency Program Graduates And Their Next Destinations

HAKAN CAKMAK
Reproductive Endocrinology & Infertility Fellowship
UCSF

AMANDA KALLEN
Reproductive Endocrinology & Infertility Fellowship
Yale University

CHARLENE HOOPER
Robert Wood Johnson Clinical Scholar

KEN-YU LIN
Gynecologic Oncology Fellowship
University of Texas Southwestern

SARAH CROSS
MFM Ultrasound Fellowship
Yale University

DANIEL PAIK
Gynecologic Oncology Fellowship
UCLA
Newest Additions to the Yale Faculty

**Ryan Martin, MD, FACOG**, joins our faculty after completing many years of training in New Haven. After graduating from Arizona State University, Ryan arrived at Yale for medical school in 1999 and remained here for residency, finishing in 2007. He completed his fellowship at Yale in the Reproductive Endocrinology and Infertility Section in June 2010, and decided to remain on faculty. Admired by clinicians for his excellent surgical skills and patient rapport, Ryan already has over 20 publications. Although we have not traditionally given awards for resident or fellow with the best sense of humor, Ryan would be high on most attendings’ lists for such an honor.

**Elena Ratner, MD**, joins our faculty after completing residency training here and finishing her gynecologic oncology fellowship here in June 2010. Elena graduated from medical school at the State University of New York at Buffalo in 2003, having previously graduated from Barnard College where she was president of the student government. Her activism continued here, where she founded the Sexuality, Intimacy and Menopause clinic in the Division of Gynecologic Oncology. Besides her enthusiasm in the OR and for the long-term care of her cancer patients, Elena is pursuing an active research interest in cancer genetics.

**Heather Lipkind, MD, MS**, is returning to the Department after a brief period in New York City. Heather was a member of the NYU contingent, having served her residency and conducted considerable research under the leadership of Dr. Lockwood. She finished her fellowship in Maternal and Fetal Medicine at Columbia, where she also received a master’s degree in Epidemiology. She then came to our MFM section. Heather moved back to NYC and joined the faculty at Albert Einstein in 2009, and we are delighted that she chose to move back to Connecticut and rejoin our faculty in 2010. Heather’s research interests include public health aspects of obstetrics.

**Julia Shaw, MD, MBA**, has been in our Department since 2004. She completed her MD at the University of Missouri, and finished her residency in Ob/Gyn at the University of Oklahoma in 1999. She remained on faculty in Oklahoma until moving to Yale in 2004, when she assumed the associate directorship of the Yale-New Haven Hospital Women’s Center. She became director of the Women’s Center in 2009 and took on a progressive leadership role as the residency associate director. In 2010 she was named director of the residency program, where she has effected many very positive changes. Julia has received numerous awards in the medical education of residents and medical students.

**Divya Patel, MPH, PhD**, joins our faculty as a member of our Comparative Effectiveness Research Group. Divya completed her PhD in Epidemiology at the University of Michigan and has been a member of the faculty in the Department of Ob/Gyn at the University of Michigan since 2004 in the Section of Health Services Research. Her primary research interests include the epidemiology of gynecologic cancers and sexually transmitted infections, with a focus on early detection and prevention. She is currently funded by a career development award through the National Cancer Institute to examine the role of host and viral factors in the relationship between human papillomavirus (HPV) and cervical pre-invasive disease. At Michigan, she mentored many students, residents and fellows and collaborated with other faculty members, publishing on pelvic floor dysfunction as well as family planning and obstetric topics. She looks forward to developing new research collaborations in the Department of Ob/Gyn at Yale.
New Fellows On Board July 1, 2010

Gynecologic Oncology: Joyce Varughese, MD
Maternal-Fetal Medicine: Christina Duzyj, MD, MPH
Maternal-Fetal Medicine: Ramesha Papanna, MD, MPH
Reproductive Endocrinology & Infertility: Leo Doherty, MD
Reproductive Endocrinology & Infertility: Saioa Torrealdy, MD
Urogynecology & Reconstructive Pelvic Surgery: Madeline Dick, MD
Urogynecology & Reconstructive Pelvic Surgery: Sallis Yip, MD

Our 2010 Fellowship Graduates and Their Next Destinations

Sarah Lee, MD
Good Samaritan Hospital – San Jose, CA

Ryan Martin, MD
Faculty of Yale University – Reproductive Endocrinology and Infertility

Elena Ratner, MD
Faculty of Yale University – Gynecologic Oncology

Mark Wehrum, MD
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology,
Womack Army Medical Center, Fort Bragg, NC
PHOTO HIGHLIGHTS FROM THE APRIL 2010 ALUMNI REUNION IN NEW HAVEN, CONNECTICUT
PHOTO HIGHLIGHTS FROM THE APRIL 2010 ALUMNI REUNION IN NEW HAVEN, CONNECTICUT
PHOTO HIGHLIGHTS FROM THE 2010 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
PHOTO HIGHLIGHTS FROM THE 2010 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
HONORING PETER E. SCHWARTZ, MD

Our YOGS gathering at the The Anlyan Center (TAC) on April 2, 2011 celebrates the career of a true Yale icon. We are honoring Dr. Peter E. Schwartz for over 40 years of dedication to our Department: to our students, physicians and patients, and to all those throughout the world whose lives he has directly saved or bettered indirectly by the thousands he has taught.

Speaking about Peter’s contributions will be six of his colleagues and former students. Although we all think about Roberto Romero as a world-famous perinatologist, Roberto still considers himself one of Peter’s first oncology fellows. Subsequent fellow David Fishman informed me that he would give a talk even if not invited – so how could I refuse? Gil Mor, the world’s only person who can make a talk about apoptosis exciting, will talk about research interests he shares with Peter, and Alan DeCherney will give an after-dinner talk at the Peabody about his longstanding friendship and collaboration with Peter. I also have to humbly note that Peter asked me to give a talk with his most recent oncology fellowship graduate, Elena Ratner, about a program we have started in the Department to care for the sexuality, intimacy and menopause concerns of gynecologic cancer survivors.

Peter came to Yale in 1967, having graduated from Union College and the Albert Einstein College of Medicine. He then traveled to M.D. Anderson for his gynecologic oncology fellowship. Returning to Yale in 1975, Peter rapidly rose through the ranks of our Department, becoming a professor in 1985. He was appointed as the John Slade Ely Professor of Obstetrics and Gynecology in 1992. Peter was the Director of Gynecologic Oncology at Yale from 1979 until 2005; he is currently the Vice Chairman, Section of Gynecology, in our Department.

But those are just his local activities. Peter is regularly honored by Good Housekeeping and Ladies Home Journal and has been named to Connecticut and New York magazines’ lists of best doctors and Castle Connolly’s America’s Top Doctors for many years. He has served as the president of the Society of Gynecologic Oncologists. Peter has also been elected as an honorary member of cancer societies in Canada, Peru and Serbia. Those are only a few of the locales for his well over 200 national and international presentations.

Peter still has had time for 400 publications, and continues to do active research in our Department. But clinical activities still occupy most of Peter’s time. He is always busy, teaching our residents and fellows (how many of us still calm ourselves in the OR repeating the mantra “Restore normal anatomy“?), answering our never-ending phone questions or OR consults, and traveling throughout the state to advance the care of gynecologic oncology patients in Connecticut.

Photo By: Harold Shapiro
IN FOND MEMORY

Marshall Holley, MD

Our Department lost one of its major stalwarts in December 2010. Dr. Marshall Holley died at the age of 75 years following a long, courageous battle with prostate cancer. Marshall was truly New Haven’s star. He was born here, graduated from Hillhouse High School, and returned to Yale for his residency in Obstetrics and Gynecology after graduating from Amherst College and Howard University School of Medicine. From 1969 until 2002, Marshall led the New Haven Ob/Gyn community in many ways. He was president of the Obstetrical Society in 1980 and pioneered collaborative midwifery practice.

Marshall was known for several other specialties. There were few uteri that needed to be removed for which he would not attempt a vaginal approach. Most Yale residents trained here towards the end of the 20th century know how to morcellate a uterus thanks to Marshall’s training. He also always had one of the lowest cesarean section rates in the community, thanks to both his outstanding midwives and his exceptional skill with forceps. Marshall always kept our residents “honest” at Grand Rounds.

Besides his wife Terry and son David, he loved his tennis. When not actively attending his patients, Marshall would be on the tennis court or promoting the game through his New England Tennis Association activities. A man of many interests, we will all miss Marshall.

Marshall’s Eulogy

(This eulogy was written by a dear friend, Dr. Emily Fine.)

When Terry asked me to say a few words about Marshall, I was hugely honored. Then I realized how daunting this would be. He truly did touch hundreds of lives. After all, Marshall was larger than life, especially during his “winter weight season,” as he would say. So I decided that the most appropriate way to honor this man I loved so dearly was to talk about “Marshall the Mentor.”

Marshall is the reason I became an Ob/Gyn. I met him in 1976 when I was a second-year medical student just beginning my clinical rotations. I was leaning towards Ob/Gyn and, lo and behold, I was assigned to Ob/Gyn for my first foray on the wards. At that time the rotation at Yale had mixed reviews, but there was a special option offered to one student: Leave the mother house of Yale and work with this well-respected but very exacting attending, a Yale-trained and highly revered person. This man had a successful private practice located in the very inner city and also worked half time for the underserved at the Hill Health Center. For his part, he was willing to teach a medical student…and this medical student would be me.

The experience was life-changing and inspiring, not just professionally but personally. It cemented my love of this specialty, but more importantly, I found a mentor and a friend for life. For six weeks I never left his side. I carried a beeper not just for the Hill Health Center, but appreciating my enthusiasm, he gave me one for his private practice as well. There were dozens of deliveries, O.R. cases and office visits. He never tired of teaching. His passion for Ob/Gyn was infectious. He worked hard and tirelessly, never complaining about his hours or lack of sleep. Of course, there was a small price I had to pay: Going to and from the hospital with him in his car meant being covered with dog drool and hair. His big dogs were always a top priority. Then there was his sartorial outrageousness, the clashing checks and stripes and the undefinable colors of his jackets so early in the morning!

The experience changed me forever. Marshall’s passion for teaching, his breadth of knowledge, his clinical acumen, his demanding and exacting style made this my peak medical school experience.
How lucky I was to have been mentored by Marshall the physician so early on! But it was Marshall the human being that was truly his greatest gift to me. His empathy and generosity of spirit were evident wherever he worked. His patients were all treated with dignity and caring – CEO, physician or a single mom from the Hill. The same was true for his colleagues. Marshall never pulled rank, and he embraced everyone equally as long as he saw that their work was done with the same integrity and compassion he demonstrated every single day. And to see his joy as a father to his beloved son David added yet another dimension to this man’s humanity.

Of course, Marshall did have a few unique quirks. How many of you realize that Marshall had a “short women” obsession? We “shorties” loved to tease him about this over the years. Seriously, if you look at his mentees, his midwives, his favorite residents and the love of his life, Terry, I think I am the giant among them at a towering 5’3”.

Another better-known Marshall quirk was his famous outspoken honesty, almost bordering on bluntness. Like the time we had lunch together during my surgery rotation and he instructed me, still a fledgling medical student, to “check out this new young surgeon Steve Stein. If I am referring patients to him, I want to make sure the hype has some foundation.” Little did he realize that checking him out would result in our 30-plus-year marriage and a lifetime of Marshall and Steve schmoozing about the Giants together – in fact, even during my second stage of labor! Or the time he delivered our first child, an event that we all know endears oneself to her obstetrician forever, at which time he commented that he “absolutely could not understand how two decent-looking people could produce a baby that ugly.” By the way, he did retract that years later, again with utter frankness.

Marshall continued to be a mentor to me throughout my residency. Our devotion to each other had been deeply cemented early on. This devout allegiance was often the case with so many of his colleagues – nurses, students and physicians alike. As a resident, the guidance was more reality-based. He would inspire me to learn my trade, hone my skills and become a thinking physician/surgeon. I strove to be the vaginal hysterectomy queen to his vaginal hysterectomy king, although I think he still beat me by at least 300 grams. No one did that procedure better. And I too have his disdain for foley catheters that I will never lose. Of course, let us not forget Marshall, the famous frugal one, intolerant of any waste! It still breaks my heart not to get at least three uses out of one suture.

The truth is that Marshall had deep-seated principles and a professionalism that spoke to medicine practiced at a higher plane. He approached all his cases methodically, using clear judgment and academic-based knowledge. He remained calm even in emergencies or when confronted with stressful situations. He never took shortcuts or backed away from a challenge. He never wasted resources, performed unnecessary services or ordered a test that would not affect his clinical decision. And he never abandoned those in need and the underserved. How could one ever wish for a better mentor?

After my residency, he became more a dear friend than a mentor. We shared many of life’s crossroads and milestones – the good and the bad. When my family had a big celebration two summers ago, commemorating four major events at once, it was Marshall who got the biggest shout-out. After all, he was ultimately responsible for it all. And I am so grateful that Steve and I spent time with Marshall and Terry in the Philippines a year ago when we went on a surgical mission there. His marriage to Terry was awesome, and to see their love flourish in the face of the hardship of his cancer was inspirational. He handled his horrific illness with calmness, dignity and grace, again showing me Marshall as the consummate mentor. He was always thankful for a life so fully lived. And I will forever be thankful for a life so fully shared. I love you Marshall.

Emily Fine


**BIRTH ANNOUNCEMENTS**

Congratulations to the Yale Ob/Gyn doctors who recently welcomed new babies:

**Alton Dulay Tiongco** – 5 pounds, 14 ounces  
January 20, 2010 (Antonette Dulay and Alvin Tiongco)

**Alexander Danil Makarov** – 7 pounds, 10 ounces  
February 18, 2010 (Jennifer Kulp and Danil Makarov)

**Julia Bell** – 6 pounds, 10 ounces  
May 9, 2010 (Erika Werner and Frazier Bell)

**Gabriella Erenna Ratner** – 6.5 pounds  
August 1, 2010 (Elena and Josh Ratner)

**Estella Rose Guess Johnson** – 5 pounds, 14.5 ounces  
August 23, 2010 (Marsha K. Guess and Joshua Johnson)

**Sera Dian Godbout** – 6 pounds, 12.5 ounces  
**Darya Marie Godbout** – 5 pounds, 3 ounces  
September 23, 2010 (Pinar Kodaman and Kevin Godbout)

**Katerina Paraskevi Sakkas** – 6 pounds, 7 ounces  
October 1, 2010 (Maria Lalioti and Denny Sakkas)
GRANTS AWARDED

**Dr. Vikki M. Abrahams** – American Heart Association – “Effect of antiphospholipid antibodies on trophoblast function and vascular remodeling in pregnant APS patients”

**Dr. Vikki M. Abrahams** – R01 National Institute of Child Health & Human Development (NICHD) – “Innate Immune Responses of Trophoblasts in Pregnancy”

**Dr. Mert Ozan Bahtiyar** – American Institute of Ultrasound in Medicine – “Fetal Cardiac Response to Intraamniotic Infection”

**Drs. Caitlin S. and Irina A. Buhimschi** – R01 National Institute of Child Health & Human Development (NICHD) – “DAMP RAGE Signaling and Fetal Injury in Inflammation-Induced Preterm Birth”

**Dr. Irina A. Buhimschi** – Bill & Melinda Gates Foundation – “Reducing preeclampsia morbidity through Congo Red Dot test”

**Dr. Kathleen A. Connell** – Yale Pepper Center on Aging – “DNA methylation of HOXA11: An epigenetic link between aging, obesity and pelvic organ prolapse”

**Dr. Sabrina Diano** – R01 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) – “A carboxypeptidase in the regulation of hypothalamic circuitry”

**Dr. Se-Te Joseph Huang** – National Institute of Child Health & Human Development (NICHD) ARRA Supplement to provide Summer Research Experiences for Students and Science Educators – “The Role of Decidual Innate Immunity in the Pathogenesis of Preeclampsia”

**Dr. Csaba Leranth** – R01 National Institute of Environmental Health Sciences (NIEHS) – “Bisphenol-A Effect on Primate Brain”


**Dr. Gil G. Mor** – United States-Israel Binational Science Foundation – “Preparation of the uterus for implantation”

**Dr. Michael J. Paidas** – Talecris Biotherapeutics – “Antithrombin levels preceding placenta mediated complications”

**Dr. Lubna Pal** – Virginia Commonwealth University – “Pharmacogenetics of Metformin Action in PCOS”

**Dr. Alessandro D. Santin** – Yale Cancer Center/Women’s Health Research at Yale – “CPE Peptide-based Nanoparticles for Ovarian Cancer Therapy”

**Dr. Emre Seli** – R01 National Institute of Child Health & Human Development (NICHD) – “Regulation of maternal mRNA translation during early development”

**Dr. Anna K. Sfakianaki** – Kenneth J. Ryan Residency Training Program – “Residency Training in Family Planning”
PRESS GANEY PATIENT SATISFACTION SURVEY

In the most recent Patient Satisfaction Survey from Press Ganey, the national leader in patient satisfaction measurement, our practices received the following scores in Overall Practice Assessment:

- Yale Urogynecology (93.2)
- Yale Maternal-Fetal Medicine (90.5)
- Yale Gynecologic Oncology (NA)
- Yale Fertility Center (91.9)

YALE OB/GYN PHYSICIANS ON 2010 TOP DOCS LISTS

In New York Magazine's annual “Best Doctors” issue, five from Yale’s Department of Obstetrics, Gynecology and Reproductive Science were recognized:

- Joshua Copel, MD (MFM)
- Charles J. Lockwood, MD (MFM)
- Peter E. Schwartz, MD (Gyn Oncology)
- Pasquale Patrizio, MD (REI)
- Hugh S. Taylor, MD (REI)

Closer to home, Connecticut Magazine identified two of our physicians as “Top Docs” in their 2010 annual survey:

- Edmund F. Funai, MD (MFM)
- Charles J. Lockwood, MD (MFM)

U.S. NEWS & WORLD REPORT NAMES YNHH ONE OF THE NATION’S TOP HOSPITALS

U.S. News & World Report named Yale-New Haven Hospital one of “America’s Top-Ranked Hospitals.” YNHH ranked among the nation’s top 50 hospitals.

RECORD NUMBER OF ALUMNI IN PRESTIGIOUS POSITIONS

It is a testament to our program excellence that so many of our faculty, fellows and residents have gone on to secure highly regarded positions in the American medical field. These include:

- 25 Chairs of Obstetrics and Gynecology
- 4 Deans of Medical Schools
- 5 Key Positions at the National Institutes of Health
- 7 Institute of Medicine Members
WHERE IN THE WORLD …

Please take a look at the list below and help us locate some of our more elusive alumni!

Stuart Adams
Colin Bailey, MD
Charles Brinkman III, MD
Marshall Carpenter, MD
Edward DeSano, Jr., MD.
Arthur Kavanagh, Jr., MD
Kenneth Kearns, MD
Andrew Krinsky, MD
Annette LaMorte, MD
Raphael Mendoza
Orlando J. Miller, MD
Jack Mobr, MD
John S. Mutterperl, MD
Ibrahim Sozen, MD

If you know their whereabouts, please let them know that we are trying to contact them to include them in our Society. Contact info may be mailed to yogs@yale.edu.

DID YOU KNOW?

Charles J. Lockwood, MD, has been elected to the Institute of Medicine (IOM) of the National Academies of Sciences. Those elected to the institute have made significant contributions to the advancement of medical science, healthcare and public health, and election is considered one of the highest honors in the health sciences.

Sonya Abdel-Razek, MD, passed the ABOG general Ob/Gyn exam.

Vicki Abrahams, PhD, was selected to receive a 2009 Preterm Birth Planning Grant from the Preterm Birth Advisory Committee and Directors of the Burroughs Wellcome Fund. The planning grant provides $50,000 from November 1, 2009 to November 30, 2010. Additionally, Vicki was recently awarded a second year under the McKern Award for her outstanding work on “Human Endogenous Retroviruses: A Novel Biomarker for Preeclampsia.”

Mert Bahtiyar, MD, received a $10K grant from the American Institute of Ultrasound in Medicine.

Catalin Buhimschi, MD, received the 2010 Plenary Session I Research Excellence Award from the Society for Maternal Fetal Medicine for his presentation entitled: “Ultrasound Measurement of Fetal Adrenal Gland Enlargement: An Accurate Predictor of Preterm Birth (PTB).” Co-authored with Ozhan Turan, Sifa Turan, Edmund Funai, Irina Buhimschi, Christopher Harman, Joshua Copel and Ahmet Baschat, this was a joint presentation with the University of Maryland School of Medicine.

Madeline Dick-Biascoechea, MD, joined the Urogynecology and Reconstructive Pelvic Surgery Section as the first-year fellow effective July 1, 2010. Madeline is a Clinical Instructor at Yale University School of Medicine. She has been an attending physician in the Women’s Care Center at Yale-New Haven Hospital since 2005.
Graciela Krikun, PhD, received additional funding from Aniara (a company that she had obtained a grant from previously). The additional funds will further her work on studying women with and without endometriosis to establish if this disease can be detectable without the need for surgery. Additionally, the Faculty of 1000 Medicine (a literature awareness service that identifies and evaluates the most important articles published in medicine based on the recommendations of a faculty of over 2,000 peer-nominated leading researchers and clinicians) notified Dr. Krikun that an article she co-authored with Zhiwei Hu, Kevin Ostee, Kaylon Bruner-Tran, Frederick Schatz, Hugh Taylor, Paolo Toti, Felice Arcuri, Williams Konigsberg, Alan Garen, Carmen Booth and Charles Lockwood entitled “The immunoconjugate ‘icon’ targets aberrantly expressed endothelial tissue factor causing regression of endometriosis” (Am J Pathol, 2010 Feb) was selected as a noteworthy publication.

At the Discovery to Cure Gala held in October, over $200,000 was raised for cancer screening for women at high risk. Gil Mor, MD, PhD, is the creator of the Discovery to Cure Program.

Errol Norwitz, MD, PhD, accepted the position as Chair, Department of Obstetrics/Gynecology at Tufts University School of Medicine. Dr. Norwitz becomes the 25th individual to chair a medical school program.

Michael Paidas, MD, recently had a paper published in the February 6, 2010 edition of The Lancet. The article, entitled “Pulmonary embolism in pregnancy,” was co-authored with Ghada Bourjelly, Hanan Khalil and Karen Rosene-Montella, all from Brown University, and Marc Rodger from the University of Ottawa.

Dr. Paidas also received this year’s David J. Leffell Prize for Clinical Excellence. Dr. Paidas was recognized at the YMG Annual Meeting in 2010. This annual award was established to recognize a YMG faculty member who best exemplifies clinical expertise, a commitment to teaching and the highest standards of care and compassion. The recipient represents the best in clinical medicine and serves as a role model for faculty peers, residents, fellows and medical students.

Chris Pettker, MD, passed the ABOG MFM oral exam.

Jill Reiter, PhD, has been named the Director of the new Perinatal Research Laboratory within the Division of Maternal Fetal Medicine at Indiana University School of Medicine in Indianapolis.

Yale’s Office of Public Affairs published a press release on Hugh Taylor, MD, regarding his team’s discovery that exposure during pregnancy to Bisphenol-A (BPA), a common component of plastics, causes permanent abnormalities in the uterus of offspring, including alteration in their DNA. The findings were reported in the March issue of the Journal of the Federation of American Societies for Experimental Biology.

Tracy Wittreich (Ob/Gyn Infertility midwife) raised over $4,500 through the March for Babies walk in April 2010.
**NETCASTS AVAILABLE ON ITUNES**

Next time you’re downloading your favorite music from iTunes, don’t forget to add a few Yale netcasts to your playlist. The number of downloadable files available is continuously increasing, thanks to the Office of Public Affairs. The netcasts include talks by alumni, faculty and other Yale-affiliated speakers. All netcasts are free from iTunes, so download them now at [http://opa.yale.edu/netcasts.aspx](http://opa.yale.edu/netcasts.aspx).

**BLOGS**


**FACEBOOK PAGES**


Yale Program for *In Vitro* Fertilization: [http://www.facebook.com/pages/Yale-In-Vitro-Fertilization-Program/88633862352](http://www.facebook.com/pages/Yale-In-Vitro-Fertilization-Program/88633862352)


DR. HAROLD R. BEHRMAN MEMORIAL LECTURESHIP FUND

In memory of Harold R. Behrman, PhD, Professor of Obstetrics, Gynecology and Reproductive Sciences, and of Pharmacology, the Department of Obstetrics, Gynecology and Reproductive Sciences has established the Dr. Harold R. Behrman Memorial Lectureship Fund. The fund’s purpose is to continue his outstanding legacy of research mentorship and to recognize Dr. Behrman’s lasting impact on his field as well as on students, fellows and faculty by bringing world-renowned researchers to the campus.

Dr. Behrman served for over 30 years on the Yale faculty and had a profound impact on this community. His research and mentoring greatly impacted the field of reproductive biology.

Below are giving details for those of you who wish to contribute to the Lectureship Fund.

GIVING INFORMATION

Attn: Joy Carrigan
Development Office
Yale School of Medicine
Box 7611
New Haven, CT 06519-0611

Checks can be made payable to: Yale School of Medicine
Memo Line: Dr. Harold R. Behrman Memorial Lectureship

DONATIONS

Our Department is constantly seeking philanthropic donations to help us fund our research and teaching missions. Examples of programs and initiatives constantly in need of support are the C. Lee Buxton Memorial Lecture, Residents’ Research Day, the Nathan Kase Annual Lecture, Gynecologic Oncology’s Discovery to Cure Program and a host of under-funded reproductive sciences research programs.

There are two ways to donate: online at https://apps.business.yale.edu/dc/obgyn/new.do or by check, payable to Yale University, mailed to:

Yale University School of Medicine
Department of Obstetrics, Gynecology and Reproductive Sciences
333 Cedar Street, PO Box 208063, FMB 337
New Haven, CT 06520-8063
Attn: YOGS Coordinator

Name: __________________________
Institution: ______________________
Street: __________________________
City: ___________________________ State: ______ Zip: ______
Country: ________________________
Donation Amount: ________________
WE WANT TO SHARE YOUR SUCCESSES!

Everyone’s favorite part of an alumni magazine is the section listing professional and personal updates, and YOGS alumni are no exception! But to keep this part of the YOGS Journal current, we need your help. If there is any news you’d like to share with your Yale family – about your career, personal achievements, family or anything you think your friends would like to know – please update us by filling out and returning the form below.

Name:  
Year:  
Street:  
City:  
State:  
Zip:  
Country:  

☐ Check if this is a new address

Tel:  
Fax:  
Email:  

Tell us your news (marriage, birth, death, career milestones, honors, etc.):

If you are advising us of an alumni death, please provide us with the following:

Name of deceased:  
Class year:  
Approximate date of death:  
Contact name and phone number:  

Does the family of the deceased wish to continue receiving mail from YOGS?  ☐ Yes  ☐ No

Please email completed form to: yogs@yale.edu or fax to 203-737-1883. Or mail to:

Yale University School of Medicine  
Department of Obstetrics, Gynecology and Reproductive Sciences  
333 Cedar Street, PO Box 208063, FMB 337  
New Haven, CT 06520-8063  
Attn: YOGS Coordinator

All submissions must be made in writing. Class notes may be edited for clarity and space. Due to limited space, the YOGS Journal cannot guarantee the publication of all items.
As a member or future member of YOGS, you may already be well aware of the many benefits membership brings – inclusion in society events, the latest Ob/Gyn news and information, invitations to lectures and workshops, and of course the annual YOGS Journal.

But to keep our Society functioning at the highest level, we need your continued support. If you’ve already paid your annual dues, thank you! If you haven’t, please take a moment to fill out the form below and return it to us with payment as soon as possible. And please consider becoming a lifetime YOGS member so you’ll never miss any of the benefits of membership.

Amount Paid: ________________________________
Date: ________________________________

YOGS MEMBERSHIP INVOICE

Name (Last)    (First)    (Middle Initial)    (Degree)
Institution/Practice Name
Street Address    Office/Suite #
City    State/Province    Zip/Postal Code    Country
Phone (____) ______________________________    Email Address ______________________________
Spouse/Partner’s Name ___________________________________________________________________

Membership Dues (please check one)
☐ One Year $150    ☐ Two Years $200
☐ Lifetime Membership $1,500

Two ways to pay:
2. By Check Payable to Yale Obstetrical and Gynecological Society (YOGS):
   Mail to:
   Yale University School of Medicine
   Department of Obstetrics, Gynecology and Reproductive Sciences
   333 Cedar Street, FMB 337
   PO Box 208063
   New Haven, CT 06520-8063
   Attn: Dianna Malvey