THE JOURNAL FOR ALUMNI AND FRIENDS OF YALE OB/GYN

Yale Obstetrical and Gynecological Society

YOGS
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ULTRASOUND ECHOES FROM 1983 TO NOW

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Who was instrumental in making Yale great in ultrasound? Most people would cite John Hobbins, based on the combination of his unique clinical gifts, creativity, optimism, selflessness, cheerful personality and constant encouragement of those around him to conduct outstanding work. But he was also adept at spotting talent, assembling a team that could work creatively. John brought together Peter Grannum, Charlie Kleinman, Greg Devore, Roberto Romero, Frank Chervenak, Philippe Jeanty and Al Reece at a time when the obstetrical ultrasound world was first developing and was wide open for exploration.

The “firsts” from the Yale Perinatal Unit are almost too numerous to count. A medical student thesis by Steve Warsof provided the first formulas for estimating fetal weight. Peter Grannum developed a reproducible way of grading the placenta and Philippe Jeanty devised a way to provide real-time ultrasound guidance for invasive procedures. Many of us teamed up to perform the first ultrasound-guided fetal blood sampling and transfusions in the U.S., and Charlie Kleinman developed a model for interdepartmental cooperation, forming the first fetal cardiovascular center anywhere, a collaboration with Pediatrics that continues today.

The first fetal echoes I performed required two ultrasounds: one for imaging and the other for Doppler. The Doppler system was a precarious rack of components taller than I am that had to be wheeled over from Radiology. There were two connections between the South and East Pavilions, each sloped a different way. I had to get the machine for every fetal echo session, and I could only take it via the corridor with a down slope—it was too heavy to push uphill. Adjusting the many control knobs simultaneously required an intelligent octopus. Now a few simple buttons and a touch screen control most of our Doppler functions.

The first vaginal transducer was given to Al Reece in the late ’80s. I remember scanning with him and being unimpressed that it added anything to our abdominal transducers. Now no Maternal-Fetal Medicine specialist would dream of practicing without one.

But the biggest name in ultrasound at Yale will always be John Hobbins. There was far more to his impact than his uncanny ability to see things on the screen that nobody else did. He was always upbeat and happy, no matter the time of day or circumstance. Once, as a first year fellow, I was on the Labor Floor at 2 AM in the middle of February with the flu and a transfer patient whose scan was very challenging. John happened to be returning from Hawaii and didn’t have a ride back to Madison, so he appeared on the Labor Floor and seemed thrilled to be scanning with me to sort everything out. He was also always good for sharing a recipe if the residents were a few minutes late for rounds.

The only person who came close to John Hobbins’ diagnostic insights was Charlie Kleinman. One of my principles became never to disagree with a diagnosis either of them made from an ultrasound. In many years working with both of them, I was never able to beat John and was only right once when Charlie was wrong.

Peter Grannum taught all of us important lessons in how to treat everybody with respect, how to work, how to teach and how to interact with patients. His calm voice saying “Hang steady” as he performed procedures remains with everyone who worked with him.
When I came to Yale in 1983 there were two ultrasound machines in the Perinatal Unit. One was a GE Dataline with a single linear array transducer. The images were so grainy you could see the raster lines down each picture, with white or black blotches creating a hazy image. The other machine was a static scanner. Only the sonographers and select faculty were allowed to touch that one. I never did.

We had only one room in 1983, with two sonographers. Friday was the fellow’s day in ultrasound, and there was no sonographer most weeks, so I did amniocenteses after doing the scanning myself by having the genetic counselor hold the transducer for guidance. Now we have four rooms in the Tompkins office and six at Long Wharf, all with “high-end” ultrasound machines, multiple portable ultrasound machines on L&B and Maternal Special Care, plus office-level machines in every exam room for prenatal visits at Tompkins and Long Wharf, not to mention our four major community hospital satellites. Any one of what we now call a low-end machine is far better than the best equipment available when I started.

It was really quite amazing how much we could see with those old systems, even though the images looked like something that came out of a snow blower. Part of the fun of being at Yale was John Hobbins’ connections to the various manufacturers and their representatives bringing new equipment by for us to play with. Most of those companies no longer exist, having been bought out by larger multinational conglomerates. Hewlett-Packard and Advanced Technology Labs (ATL) are now part of Philips; Acuson disappeared into Siemens; GE first abandoned ultrasound, then bought Corometrics, Vingmed and Voluson to become a major player in the current market. One of the old ATL machines had a computer game, Pong, embedded in the software. If you took off the cover and flipped a couple of relays, you could turn it into what we thought was a pretty sophisticated game at the time.

What was once exotic is now routine. Every machine has color, pulsed and power Doppler as well as 3D/4D, options that were once available on only a few of the machines. I am sure that the faculty and fellows cannot dream of scanning without all these options. Whenever they seem impressed at my seeing details in a scan, I smile to myself thinking about the images I had to decipher when I started.

As I write this, I recall that Peter Grannum died 19 years ago. John Hobbins’ last night on call was the night my son was born almost 18 years ago. Is thinking about ultrasound at Yale just an exercise in nostalgia? Not really. Since the days of those cited at the beginning of this article, we have trained another generation of leaders in ultrasound, including Ray Bahado-Singh, Alfred Abuhamad and Giancarlo Mari. So stay tuned; more will follow.

Peter Grannum (right) and Al Reece perform a fetal transfusion
EDITOR’S NOTE

The following articles represent the Grand Rounds presentations of our Visiting Professor for the C. Lee Buxton Residents’ Research Day and a selection from among the remaining presentations given throughout the year.

Dr. John DeLancey spoke at our annual Residents’ Research Day on the biomechanics of birth and subsequent pelvic floor disorders. As a national leader in urogynecology practice and research, his talk provides a unique perspective.

Dr. Alessandro Santin, who joined our Gynecologic Oncology faculty two years ago, updates us on his exciting research on cervical cancer vaccines; Dr. Santin is very interested in prevention and immunological therapies.

Dr. Masoud Azodi has given us an exciting opportunity: not only are we presenting the text of his Grand Rounds, but we will also be providing you with the web reference to view the truly astounding videos of his robotic pelvic surgery. Watching him perform an endometrial cancer hysterectomy on a patient with a BMI of well over 40 truly makes you a believer in the technique.

Dr. Errol Norwitz, Co-Director of the Division of Maternal-Fetal Medicine, addresses the very controversial topic of Cesarean Delivery on Maternal Request (CDMR). CDMR is an important issue for currently practicing obstetricians, and Errol outlines the practical and ethical considerations involved. He also addresses some of the concerns raised by Dr. DeLancey regarding the role played by the route of delivery on pelvic floor support.

Finally, Dr. Sharon Phelan gives a wonderful presentation on how to help prevent endometrial carcinoma, discussing not only the medical matters inherent in dealing with obesity, but also how to help patients psychologically deal with their weight issues.

As you can tell, our Grand Rounds cover a wide swath of Ob/Gyn territory, and our guest speakers are well-respected experts in their respective fields of concentration. We will continue with our tradition of bringing nationally and internationally renowned experts to our Grand Rounds Program, and to update you on a selection from the year’s presentations. In other sections of the Journal, we share the abstracts of the graduating residents’ presentations and those of our faculty from recent scientific meetings. Please let us know if you’ll be presenting at a meeting, and we’ll be sure to note it in the News Section.
RESIDENTS’ RESEARCH DAY VISITING PROFESSOR GRAND ROUNDS

Biomechanics of Birth: Prolapse, Parturition and the Pelvic Floor

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If we knew that 10% of 3,000,000 healthy young women were being seriously injured each year, a national campaign would be launched to stop these injuries. In fact, this rate of injury to the levator ani muscles occurs during vaginal birth, yet our understanding of the nature of the injury and its common sequelae is only now being clarified. If we wish to reduce the birth-associated problems of prolapse and incontinence through injury prevention at delivery, we must know the answer to the following question: What injury occurs during vaginal birth that stays latent for many years, but results in the increased occurrence of pelvic floor disorders later in life (1)? This issue primarily concerns pelvic organ prolapse (2).

Pelvic organ prolapse is the most strongly birth-associated pelvic floor disorder. Women having two births have a relative risk of 8.0 for developing prolapse as compared to nulliparas (3), while the odds ratio for women delivering vaginally compared with women delivered by cesarean section has been reported as 2.4 (4). Prolapse is also the pelvic floor disorder that requires the most complex and failure-prone surgery to repair. Fortunately, technological developments in advanced soft-tissue imaging and biomechanical computer modeling have improved our understanding of the pathogenesis of these disorders. This article will summarize the insights made in our unit over the last decade that have resulted from the collaboration between biomechanical engineers and obstetrician/gynecologists trying to understand the biomechanics of birth and their sequelae.

About 10 to 15 years ago, magnetic resonance imaging (MRI) studies of maternal soft tissues after vaginal delivery were used to investigate the status of specific pelvic floor structures. In a study of 160 primiparous women, we found that 32 (20%) exhibited damage to the levator ani muscles on MR scans (Fig. 1) (5). None of the 80 nulliparous women serving as controls had injuries, thereby identifying birth as a cause of the type of levator ani muscle injury seen in women with pelvic floor dysfunction. This study oversampled for stress urinary incontinence; after taking this into account, it can be estimated that approximately one in 10 women delivering their first infant will sustain levator damage.

It was not clear at that point whether this injury was important long-term. Indeed, it might be a normal consequence of pregnancy in some women, like stretch marks or the change in appearance of the uterine cervix. To determine its significance, we compared the occurrence of injuries to the levator ani muscles in 151 women with prolapse and 135 women with normal pelvic organ support who were of similar age, race and hysterectomy status (6). Using MRI imaging, women with prolapse were found to be far more likely to have major levator ani defects (involving more than 50% of the muscle) than women with normal support (55% compared with 15.6%) (Fig. 2). Of women who reported delivery by forceps, 53% had major defects compared with 28% for the non-forceps women. These defects were associated with measurable loss of levator function.
Women with prolapse generated less vaginal closure force during pelvic muscle contraction than did controls (2.0 vs. 3.2 Newtons, p<.001), and those with defects generated less force than did women without defects (2.0 vs. 3.1 Newtons, p<.001). This established the strong association between prolapse and an increased occurrence of levator ani muscle injury. Of interest, in a similar case-control study that compared women with and without stress urinary incontinence, no difference between these two groups was found; this was consistent with the newly appreciated fact that the primary factor associated with stress incontinence is poor urethral closure function and not urethral support (7).

Of course, knowing how and why these muscle injuries occur is of primary importance. The use of forceps, anal sphincter laceration and episiotomy increased the odds ratio for levator muscle injury by 14.7-, 8.1-, and 3.1-fold, respectively (8). Women with levator injuries were 3.5 years older and had a 78-minute longer second stage. These morphological studies identified the role of vaginal birth in the injury and indicated where some of the damage was occurring, but did not yield information about the exact mechanism(s) of injury. This has direct clinical importance. To plan prevention efforts, we need to know why the muscle is dysfunctional. Is it due to muscle tears or nerve compression, or is it due to stretching that causes the muscle to avulse from the bone? If nerve compression is the mechanism of injury, shortening the time of compression would be important. On the other hand, if too rapid stretching of the muscle is the mechanism, slowing down the stretching would be needed. Knowing what to do depends on knowing what causes the injury.

We investigated the muscle stretch hypothesis using a geometric model (Fig. 3). This research has suggested that some muscle damage during the second stage of labor may come from overstretching because those parts of the muscle that are stretched the most are those parts that are seen to be injured (9). The pubovisceral (pubococcygeal) muscle, the shortest and most medial levator ani muscle, had the largest tissue strain with a stretch ratio of 3.26. Regions of the iliococcygeus, pubococcygeus and puborectalis muscles reached maximal stretch ratios of 2.73, 2.50 and 2.28, respectively. These values considerably exceed the maximum stretch ratio of 1.5 tolerated by striated muscle in non-pregnant animal preparations.

Tissue stretch ratios were found to be proportional to fetal head size. For example, increasing fetal head diameter by 9% increased medial pubovisceral stretch by the same amount. This analysis revealed that the region of muscle injured most often, the pubovisceral (pubococcygeal) portion, was the portion of the muscle that underwent the greatest degree of stretch. The second area of observed injury, the iliococcygeal muscle, was the muscle stretched second most. Furthermore, when the portion of the muscle at risk was identified in cross-sections cut in the same orientation as axial MR scans, the pattern of predicted injury matched the injury seen in these MR scans (Fig. 4).

There is a considerable body of data concerning the behavior of biological soft tissues under loading, yet data concerning the pelvic floor tissues during birth are only now being explored. This is a fruitful area of research, one in which major discoveries will likely be made in the near future. This type of research should provide a framework for understanding issues such as the effect of the differing rates of tissue distention and tissue rupture and strategies for changing the tissues to lessen the likelihood of injury.
Figure 1.
(a) The axial proton density magnetic resonance scan shows a normal pubovisceral muscle with the muscle outlined at the level of the mid-urethra. The scan shows the pubic symphysis (PS), urethra (U), vagina (V) and rectum (R). (b) A similar image from a woman with complete loss of the pubovisceral muscle (expected location of pubovisceral muscle shown by outline). Copyright by DeLancey 2005. Reproduced by permission (5).

Figure 2.
The occurrence of different degrees of levator ani muscle injury (major and minor) in women with pelvic organ prolapse and those with normal support (6).

Figure 3(a).
Simulated effect of fetal head descent on the levator ani muscles in the second stage of labor. At top left, a left lateral view shows the fetal head (as a sphere) located posteriorly and inferiorly to the pubic symphysis (PS) in front of the sacrum (S). The sequence of five images at left shows the fetal head as it descends 1.1, 2.9, 4.7, 7.9 and 9.9 cm below the ischial spines while the head passes along the curve of Carus (indicated by the transparent, light blue, curved tube). The sequence of five images at right shows front-left, three-quarter views corresponding to those shown at left.
Figure 3(b).
The upper bar graph compares, by muscle, initial and final muscle lengths corresponding to 1.1 and 9.9 cm model fetal head descent, respectively. The lower bar graph shows the maximum corresponding stretch ratio found in each levator ani muscle band. Note that the value of the stretch ratio is not simply proportional to initial or final length. For both graphs, muscles are arranged left to right, in ventral to dorsal order of origin location. Copyright by Biomechanics Research Lab, University of Michigan, 2003. More technical details may be found in Reference 9.

Figure 4.
(a) Normal anatomy in an axial mid-urethra proton density MRI that shows the normal pubovisceral muscle (asterisks). (b) Woman who has lost a part of the left pubovisceral muscle (displayed on the right side of the image, according to standard medical imaging convention), with lateral displacement of the vagina into the area normally occupied by the muscle. The arrow points to the expected location of the missing muscle. (c) Axial, mid-urethral section through the arch of the pubic bone [see pubic symphysis (PS), top] and the model levator ani muscles corresponding to those from the patient shown in (b). Intact muscles are shown in dark gray. The location of simulated pubovisceral muscle atrophy is illustrated by the light gray shading of the left-hand pubovisceral muscle. This location is shown to correspond with the location of muscle atrophy demonstrated in (b). OI, obturator internus; PB, pubic bone; U, urethra; V, vagina; R, rectum. Modified from Reference 9.
REFERENCES


Cervical cancer is the second most common cause of cancer-related deaths in women worldwide, with about 450,000 new cases diagnosed each year. In the United States, as well as in other industrialized countries, cervical cancer remains an important health problem for women, especially in underserved and minority groups. Although localized cervical cancer can be cured by radical surgery or radiotherapy with similar effectiveness, overall up to 35% of cervical cancer patients will experience persistent/recurrent metastatic disease for which treatment results remain poor. Thus, novel therapeutic strategies effective in the treatment of recurrent metastatic cervical cancer remain desperately needed.

In the last few years, a strong and specific association between human papillomavirus (HPV) infection and cervical cancer has been established by a multitude of epidemiological studies. Accumulating evidence suggests that the majority of cervical squamous cell carcinomas (SCCs) and a large proportion of adenocarcinomas share a common pathogenesis involving infection with the oncogenic HPV types 16 and 18. E6 and E7 transforming oncoproteins of these high-risk HPV genotypes play a crucial role in both transformation and maintenance of the malignant phenotype, and are detected in a large majority of HPV-positive cancer biopsies and almost all HPV-containing cell lines. Hence, these viral proteins represent ideal candidates as potential tumor-specific target antigens for cervical cancer immunotherapy.

Fully mature dendritic cells (DCs) are the most potent antigen-presenting cells present in the human body, and autologous DCs loaded with HPV antigens have consistently been shown to induce effective activation of the human immune system against E6 and E7 oncoproteins in vitro and more recently in vivo. Our group has recently completed multiple Phase I clinical trials evaluating the safety and immunogenicity of HPV16 or HPV18 E7 antigen-pulsed mature DC vaccination in patients with cervical cancer. In our most recent report, we investigated whether HPV16 or HPV18 full-length E7 antigen-pulsed mature monocyte-derived autologous dendritic cell vaccination can generate or boost an anti-E7 immune response in patients with stage IB or IIA cervical cancer. In addition, the effect of the dose of E7-pulsed DCs on the immune response elicited in cervical cancer patients was evaluated. Safety, toxicity, delayed type hypersensitivity (DTH) skin test reactions and induction of serological and cellular immunity against HPV16/18 E7 were monitored.

In preclinical studies with E7-loaded DCs, we observed an efficient induction of antigen-specific T cells from cervical cancer patients as well as from healthy individuals. Autologous DCs pulsed with full-length E7 oncoprotein of the HPV genotype involved in the disease offer the significant advantage of potentially presenting multiple immunogenic cytotoxic T lymphocyte (CTL) epitopes, as well as allowing DCs to tailor those peptides fitting self Human Leukocyte Antigen (HLA) molecules without the necessity for previous knowledge of the individual HLA type.

Because HLA class I and class II gene products are critical in the regulation of immunity against viral infections, and consequently play an important role in the control of the course of HPV infection and disease, this approach, unlike...
HPV-peptide-based vaccinations, may be more practical for large-scale vaccination protocols. Furthermore, because the selective loss of one HLA-restriction element on cervical tumor cells is a much more frequent finding than the total loss of HLA expression, it is likely that the use of full-length E7 oncoprotein-based vaccination, presenting peptides potentially capable of binding multiple HLA class I restriction elements, might be a superior form of vaccination. Consistent with this view, in the human setting, recombinant, full-length E7-pulsed autologous DCs are consistently able to elicit specific CD4+ and CD8+ CTL responses against E7-infected autologous tumor target cells in HLA-unselected patients harboring HPV16- or HPV18-positive cervical cancer in vitro as well as in vivo.

In a recent Phase I study we evaluated the safety and immunogenicity of HPV16 or HPV18 E7 antigen-pulsed mature DC vaccination in patients with early stage (i.e., stage IB-IIA) cervical cancer. Escalating doses of autologous DCs (i.e., 5, 10 and 15 x 10⁶ for injection) were pulsed with recombinant HPV16/18 E7 oncoproteins and keyhole limpet hemocyanin (KLH, a control antigen) and delivered through a total of five subcutaneous anterior thigh injections at 21-day intervals to 10 cervical cancer patients with no evidence of disease after radical surgery. We have investigated serologic responses in the vaccinated patients by a highly sensitive and specific antigen capture ELISA. In our patient cohort, we could define E7-specific antibody responses that were de novo induced following DC vaccination in five of the 10 patients. These five patients boosted their E7-specific antibody response after vaccination. Importantly, all five patients with no measurable antibody titers against E7 before vaccination responded with an increased humoral response against E7 after immunization. Similarly, progressively higher levels of KLH-specific antibody titers were detectable in 10 out of 10 patients after vaccination treatment with the immunological tracer molecule KLH. Of interest, the mean increase in antibody titer against E7 and KLH, respectively, was similar at all DC doses.

Cellular immune responses towards viral/tumor-associated antigen are considered crucial for anti-tumor effects in vivo. In order to dissect the cellular immune response induced by the E7-pulsed DC-based vaccination, we separated the PBL collected before and during the vaccination treatment into the CD4+ and CD8+ T cell compartments. CD4+ Th1 cells are considered key players for the generation of potent CTL immune responses against tumor cells, and the inability to mount and/or maintain effective antitumor/antiviral immune responses in vivo has often been attributed to the lack of generation of sufficient tumor-specific T cell help.

Although we found considerable inter-patient variability to the vaccine, we observed a significant increase in the number of IFN-γ secreting CD4+ T cells in 10 out of 10 of our immunized patients, with eight out of 10 also demonstrating a progressive increase in the number of circulating IFN-γ-secreting CD8+ T cells by ELISpot. Remarkably, all immunized patients also responded with increased titers of E7 specific antibody. These immunologic results further support the notion that the activation of CD4+ T cells, particularly IFN-γ producing Th1 cells, is critical for the simultaneous activation in vivo of the humoral and cellular arms of the immune system against HPV-infected tumors in vivo. Similarly, a significant increase in the numbers of IFN-γ-secreting KLH-specific CD4+ and CD8+ T cells in 10 out of 10 of our immunized patients was demonstrated. Thus, immunization of cervical cancer patients whose tumors expressed HPV16/18 with a DC-based vaccine may be an effective method to elicit both tumor-specific T cell and antibody immunity against HPV E7 oncoproteins in vaccinated individuals.

To rule out the presence of immunosuppression before vaccination as well as to confirm the successful induction of systemic immunity against E7 and KLH in vivo, all cancer patients were tested with a panel of recall DTH antigens in addition to E7 and KLH. Before immunization, all patients were able to respond to at least one
recall antigen while in no patient did we detect positive DTH against E7 and KLH. In contrast, although with considerable inter-patient variability, positive DTH reactions against HPV16 and 18 E7 and KLH antigens were consistently identified after vaccination in all patients. Collectively, these results indicate systemic cellular immune reaction to E7 and KLH antigens, suggesting that this therapeutic vaccination strategy may stimulate strong immunity against HPV-infected tumor cells \textit{in vivo} in patients who had previously failed to clear HPV16/18 cervical lesions.

The safety of the vaccination approach described here, combined with the potential to increase host immunity against HPV-infected tumor cells, may enable the immune system to clear a limited tumor burden and/or prevent disease recurrence in immunocompetent cervical cancer patients. Consistent with this view, 10 out of 10 (100\%) of the vaccinated cervical cancer patients in this trial remained free of disease at three years from the end of vaccination. Phase II trials of human papillomavirus E7 antigen-pulsed dendritic cell vaccination for treatment of patients with stage IB or IIA HPV16/18-infected cervical cancer are warranted.
RELATED REFERENCES


The objective of the Grand Rounds is for the participant to:

1. Be familiar with the technique of radical trachelectomy for the management of cervical cancer and to identify the suitable candidates for radical trachelectomy.

2. Know the role of minimally invasive surgery in gynecologic oncology (conventional laparoscopy versus robotic-assisted laparoscopy).

3. Be familiar with our experience with robotic surgery at Yale Gynecologic Oncology.

1. Radical trachelectomy

Patients with FIGO stage IA1 (with lymph vascular space invasion), stage IA2 or stage IB1 squamous or adenocarcinoma of the cervix who desire preservation of future fertility are candidates for radical trachelectomy. Lesions less than or equal to 2 cm in diameter with limited upper endocervical involvement are ideal candidates for vaginal radical trachelectomy. Pre-operative MRI and PET scans are especially recommended in adenocarcinoma and high-grade lesions.

Radical trachelectomy has been popularized by Professor Daniel D'Argent. Major steps for radical vaginal trachelectomy include laparoscopic lymphadenectomy, laparoscopic parametrial dissection and vaginal parametrectomy. We identify and remove the sentinel nodes prior to performing complete laparoscopic pelvic lymphadenectomy. More than 600 cases of vaginal radical trachelectomy and more than 100 cases of abdominal radical trachelectomy have been reported in the literature. We have performed one radical trachelectomy with preservation of uterine vessels using robotic technology.

The most challenging part of the procedure is to identify and isolate the ureters within the bladder pillar. After mobilizing the ureter, paracervical and parametrial tissue is resected. Frozen section is necessary to ensure an adequate endocervical margin. Finally, a permanent cerclage is placed in the remaining cervical tissue and vagino-cervical mucosa is re-approximated.

At the Eighth International Gynecologic Cancer Society (IGCS) meeting in Buenos Aires in October 2000, the experiences of 224 patients with radical vaginal trachelectomy were reported with a 30-month follow-up. The recurrence rate was only 3.1% with an acceptable pregnancy rate; however, there were increased rates of second trimester loss and pre-term delivery. To date, 603 cases of radical vaginal trachelectomy have been reported with a recurrence rate of 4.5%.

The conclusion is that the risk of recurrence is unchanged compared to radical hysterectomy, and fertility is preserved with increased rates of second trimester loss and pre-term delivery.

2. Why should we consider minimally invasive surgery instead of laparotomy in gynecologic oncology?

The benefits of minimally invasive surgery include reduced blood loss, shorter hospital stay, faster recovery and less scarring. The exploration of the entire abdomen, including the sub-diaphragm, can be accomplished adequately with the laparoscope rather than having a large vertical incision. Several prospective studies have confirmed the safety and efficacy of microinvasive surgery in oncology patients. Additionally, several retrospective and prospective randomized trials have compared
laparoscopy to laparotomy and have shown equivalent outcome in the management of gynecologic cancer. Laparoscopic surgery meets the standards of oncology surgery.

The learning curve with conventional laparoscopy is very long for a sophisticated procedure, including high periaortic lymph node dissection, resection of the parametrium and fine dissection in the pelvic sidewall. The cons of conventional laparoscopy include limited degree of motions that are also counterintuitive, a two-dimensional monitor and the awkward operating position that leads to surgeon fatigue and unsteady images. These drawbacks can cause a lack of precision and maneuverability.

The advantages of robotic surgery are that the surgeon controls the robot arm remotely, the surgeon directs the precise movements of the instrument using the console controls and the instrument moves like a human wrist, allowing increased dexterity, maneuverability and precision. With robotic surgery, the console has a three-dimensional image of the surgical field with a tenfold magnified view, which makes the tissue planes and the neurovascular bundles more visible. The stable camera platform improves the precision of the procedure. With the movements scaled down to a factor of 5:1, the robot is able to filter out hand tremors and allows the performance of fine detail during the surgery. Use of the robot for gynecologic laparoscopic surgery was cleared by the FDA in 2005.

We have prospectively followed our first 100 robotic cases at Yale Gynecologic Oncology. From September 2006 to September 2007, we performed 100 cases for benign or malignant indication. In the benign group, we had six cases that underwent risk-reducing prophylactic salpingo-oophorectomy along with hysterectomy, 20 with uterine myoma and/or menorrhagia and 33 cases with post-menopausal complex adnexal mass. The cases for gynecologic oncology included 8 for atypical complex hyperplasia of the endometrium, 7 cervical carcinoma, 18 endometrioid endometrial adenocarcinoma, 5 uterine papillary serous carcinoma and 6 cases with either ovarian or primary peritoneal carcinoma.

The mean age of our patients was 56 years (range 38-81). There were multiple co-morbidities, including hypertension, COPD, diabetes, coronary artery disease, history of DVT, PE, hypothyroidism, atrial fibrillation and multiple patients with connective tissue disorder. Patients also had a history of multiple surgeries, including multiple cesarean sections, open and laparoscopic appendectomy, cholecystectomy and open or laparoscopic procedure for endometriosis. The mean weight of our group was 192 pounds (range 121-306) (BMI range of 23-47) with four patients in excess of 300 pounds. Our mean estimated blood loss (EBL) was 165 cc; however, 46 patients had an EBL of less than 100 cc. The mean specimen weight was 220 grams (range 80-1,050). The operative time from insertion of the uterine manipulator to closure of skin incision was 2½ hours for malignant indication and 2 hours for benign procedures. The patient positioning time was between 6 and 15 minutes with incision time to docking of 8-16 minutes. The average operative time for hysterectomy and removal of the ovaries was 1 hour. None of our first 100 cases were converted to laparotomy. The mean hospital stay was 1.2 days with 67% of patients discharged on post-op day 1, and 18% on post-op day 2.

Our conclusion is that the robotic laparoscopic technique can be applied successfully to the gynecologic oncology service in the academic institution when teaching fellows and residents. The da Vinci Surgical System improves the safety and accuracy of the microinvasive approach.

3. Our experience with management of uterine cancer

In the past, endometrial cancer was treated with intracavitary iridium packing, followed by external beam radiation, followed by surgery. However, this has changed over time. In 1988,
FIGO classification changed to surgical staging with lymph node dissection. Several studies have shown favorable outcome with lymphadenectomy without radiation; others have suggested that more extensive lymph node dissection may also have therapeutic benefits. Poor prognosis for endometrial cancer in the elderly is postulated to be due more to aggressive histological type and poor immunologic defense against the cancer at an advanced age. However, less aggressive therapy in the elderly is thought to be a significant contributor to poor prognosis. This issue can be solved with incorporation of microinvasive surgery, and we believe that we can be more aggressive with surgery and lymph node dissection using this technique, including conventional and robotic assisted laparoscopy.

A recent SGO survey showed that 49% of gynecologic oncologists use laparoscopy to stage endometrial cancer. Morbid obesity is not only a major risk factor for developing endometrial cancer, but also is the leading limitation for conventional laparoscopic surgery and para-aortic lymphadenectomy in patients with endometrial carcinoma. We believe that, with robotic assisted laparoscopic surgery, we are able to manage the morbidly obese patient with uterine cancer with significantly less morbidity. From October 2006 until November 2008, we managed 85 cases of uterine cancer using robotic assisted laparoscopy. The mean age of our patients was 61, with a mean BMI of 34 kg/m² (range 19-63). Forty-one percent of our patients were morbidly obese and 25% were super-obese with a BMI of greater than 50 kg/m². Ninety-eight percent of our patients had a hysterectomy and bilateral salpingooophorectomy (two patients had a hysterectomy at an outside institution). Ninety-six percent underwent a bilateral pelvic lymph node dissection and 58% of patients had para-aortic lymph node dissection. Fourteen percent of our patients had infracolic omentectomy for staging of their cancer. Concurrent laparoscopic procedures included one appendectomy, one ventral hernia repair and one sacrocolpopexy with mesh. One patient had a bilateral mastectomy and TVT with anterior and posterior repair along with our surgical staging for uterine cancer. Estimated blood loss on average was 123 mL (range 100-400).

The average number of lymph nodes resected was 9.9 in the right pelvis, 9.6 in the left pelvis, 4.1 in the right para-aortic area and 4.6 in the left para-aortic area, which is adequate. Sixty-eight percent of our patients had stage I, 7% stage II, 7% stage IIIA and 12% stage IIIC with positive lymph node metastasis. Mean hospital stay was 1.3 days (range 0-9 days). Ninety percent of our patients were discharged from the hospital on post-op day 1 or sooner. Longer hospitalizations were indicated for medical co-morbidities and in a few patients for conversion from heparin to coumadin. None of our cases were converted to open surgery.

Our conclusion is that the robotic assisted laparoscopic staging of endometrial cancer is feasible in the academic setting with no increase in complication rate, and robotic assisted surgery makes microinvasive surgery applicable in patients with morbid obesity.

We additionally compared a single surgeon’s experience with laparotomy, conventional laparoscopy and robotic assisted laparoscopic surgery for management of endometrial cancer. We looked at 30 consecutive patients who underwent laparotomy prior to introduction of the robot and 30 consecutive patients who underwent conventional laparoscopy (15 of them prior to the robotic system being available and 15 after the robotic system became available). The mean age of the patients was equivalent in all three groups. The median BMI was 34 in the robotic surgery group, 31 in the conventional laparoscopy group and 34 in the abdominal hysterectomy group. The mean hospital stay was one day in both robotic surgery and conventional laparoscopy; however, in the laparotomy group the mean hospital stay was three days. The lymph node counts were equivalent in all three groups. Estimated blood loss was equivalent in both the robotic and conventional...
laparoscopic surgery groups (120 and 150 cc); however, it was 300 cc in the laparotomy group. The complication rates, lymph node counts and morbidities were similar in all three groups.

In conclusion, we believe that microinvasive surgery has a significant role in the management of gynecologic cancer, especially uterine cancer, cervical cancer and the management of adnexal mass. It significantly decreases morbidity and hospital stays for our patients. I would like to reemphasize, however, that what most determines the route and outcome of surgery is the surgeon and not the tools. Therefore, even though microinvasive surgery has the potential to decrease morbidity, I believe that the surgeon still remains the main determinant of the outcome.

NOTE: Our extensive experience at Yale Gynecologic Oncology is summarized during an eight-minute video of the robotic radical trachelectomy, which can be accessed at:

http://medicine.yale.edu/obgyn/gynonc/mira2009.aspx
RELATED REFERENCES: ENDOMETRIAL CANCER


RELATED REFERENCES: CERVICAL CANCER


Cesarean Delivery on Maternal Request

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“Cesarean delivery on maternal request” (CDMR)—also referred to as “patient choice cesarean”—refers to a primary cesarean delivery performed at term because the mother requests this method of delivery in the absence of conventional medical or obstetric indications (1, 2). The prevalence of CDMR is 1%-18% of cesarean deliveries worldwide and 1%-3% of cesarean deliveries in the U.S. (2, 3). These are crude estimates since birth certificates and discharge codes do not usually indicate whether a cesarean was performed on maternal request. The prevalence of the procedure appears to be increasing and is correlated with increasing affluence. CDMR remains a controversial and politically charged issue.

CONFLICTING ETHICAL PRINCIPLES

The right to be actively involved in treatment decisions, including method of delivery, is now widely accepted by physicians and patients. It has become increasingly common in all fields of medicine for patients to request a particular therapy. If the preferred therapy is one of several medically accepted options, it is unlikely to create an ethical dilemma. However, if the requested therapy has no clear medical indication, no proven benefit and/or is particularly dangerous, the patient’s right to choose is less clear.

Obstetric care providers are in a particularly precarious position, since they are responsible for the well-being of both the mother and the fetus. On occasion, conflict between the well-being of the mother and the well-being of the fetus will set in place an ethical dilemma, which can only be resolved in favor of one party and, by extension, to the detriment of the other (4). In such situations, it is important to weigh carefully the risks and benefits of each therapeutic option and to make every effort to involve the patient and her family in all aspects of the decision-making process. CDMR may also create an ethical conflict between the patient’s right to autonomous decision-making and the physician’s right to autonomy in practicing according to accepted procedures (2). The competing ethical claims that contribute to the physician’s dilemma can be summarized briefly as follows:

1. Patient autonomy, which refers to the situation in which an individual determines his or her own course of action and requires the freedom to deliberate, choose and act. Contemporary medical ethical theory has emphasized the role of patient autonomy in medical decision-making. Indeed, patient autonomy provides the ethical basis for informed consent, the recognition that patients may refuse even life-saving treatment, and the principle of truth telling, which includes the necessity to inform patients about all therapeutic options. Based on this ethical principle, the mother requesting CDMR is acting altruistically. She is prepared to assume additional risks to herself associated with cesarean delivery to avoid small risks to her fetus.

In legal terms, pregnant women (including minors) fall into the class of persons considered “competent.” As such, the principle of autonomy supports the active involvement of such women in decisions concerning method of delivery. There are several examples of clinical situations in which elective cesarean delivery prior to the onset of labor is not only acceptable but indeed recommended, including non-reassuring fetal testing (despite data showing that a non-reassuring fetal heart rate
pattern prior to labor has a 99.9% false-positive rate in predicting hypoxic-ischemic encephalopathy and the subsequent development of cerebral palsy) (5), prior cesarean delivery, breech presentation, fetal macrosomia, suspected placenta accreta, and HIV infection with viral load >1,000 copies/mL. In these situations, it is argued that the benefit to the mother and/or the fetus of abdominal delivery clearly outweighs the risk to the mother of cesarean delivery. There are also several clinical settings in which cesarean delivery may be preferable to attempted vaginal delivery, but definitive data are still lacking. These include multiple pregnancy (especially high-order multiple pregnancies), maternal hepatitis C infection, severe preeclampsia/eclampsia remote from term, and certain fetal congenital anomalies (such as gastroschisis and neural tube defects).

Importantly, the decision regarding whether or not to proceed with CDMR should not be based on financial considerations. That said, it is reassuring to note that adoption of a policy of routinely acquiescing to a request for CDMR is unlikely to have a significant impact on the overall costs of obstetric care (6).

2. **Beneficence**, which refers to the desire by the obstetric care provider to do good, and **non-maleficence**, also known as the ethical principle of *primum non nocere* (“first do no harm”).

3. **Professionalism**, which refers to the responsibility of the physician to act both as a professional and as an autonomous moral agent. While a physician may rightfully refuse to acquiesce to a request if the risk of the intervention is very large (life-threatening), if the benefit to be gained is very small and/or if a person’s request creates a potentially harmful situation for another individual, it is not clear whether any of these arguments can be used to decline a parturient’s request for CDMR. Indeed, refusal to perform CDMR on the basis of this argument can be seen as paternalistic, where paternalism refers to “refusal to accept or to acquiesce in another person’s wishes, choices or actions for that person’s own benefit.” Every effort should be made to avoid paternalism.

**POTENTIAL BENEFITS OF PLANNED CESAREAN**

Potential advantages of scheduled cesarean delivery to the mother and/or the fetus include:

- **Known endpoint for the pregnancy.** A planned cesarean delivery is usually scheduled. A known endpoint to the pregnancy facilitates issues related to work, child care and help at home for the mother and her partner. It also provides an opportunity to schedule surgery with a particular provider.

- **Avoidance of post-term pregnancy.** Planned cesarean deliveries are typically scheduled between 39 and 40 weeks of gestation. Thus, post-term pregnancy (defined as a pregnancy continuing beyond 42-0/7 weeks of gestation), which is associated with higher rates of perinatal morbidity and mortality than pregnancies delivering at term, can be avoided.

- **Reduction in risk of postpartum hemorrhage.** The majority of evidence shows a lower risk of postpartum hemorrhage with planned cesarean than with both planned vaginal delivery and unplanned cesarean delivery.

- **Reduction of risks associated with unplanned surgery.** An emergency cesarean delivery is often a traumatic experience for women, and has been associated with postnatal depression and posttraumatic stress. Emergency surgery is also associated with higher maternal and fetal risks than elective surgery, including infection, accidental injury to abdominal organs, fetal laceration during hysterotomy, hemorrhage and anesthesia-related complications.
• **Prevention of late stillbirth.** Once the fetus is delivered, it is no longer at risk of intrapartum fetal demise (stillbirth). It is estimated that between one in 50 and one in 500 fetuses reach maturity **in utero** and are subsequently involved in a catastrophe resulting in severe neurologic damage or perinatal death (7).

• **Reduction in non-respiratory neonatal disorders.** Cesarean delivery prior to the onset of labor reduces or eliminates fetal morbidity and mortality related to the process of vaginal birth. Intrapartum complications that are potentially reduced or avoided include brachial plexus injury related to shoulder dystocia, bone trauma (fracture of clavicle, skull, humerus) and asphyxia related to intrapartum events (e.g., umbilical cord prolapse, placental abruption).

• **Reduction in risk of pelvic floor injury.** Fear of perineal injury and urinary and fecal incontinence from labor and vaginal delivery is a common reason for CDMR; however, these concerns are not based on high-quality evidence. Fewer women have urinary incontinence in the months after planned cesarean delivery, and urinary incontinence rates two and five years after delivery are not significantly different between women who planned cesarean delivery and those who planned vaginal births. In addition, planned cesarean delivery does not appear to confer protection against fecal incontinence compared to planned vaginal delivery.

**POTENTIAL DISADVANTAGES AND RISKS OF PLANNED CESAREAN**

Scheduled cesarean delivery may pose some disadvantages or risks to the mother and/or the fetus, including:

• **Longer recovery period.** The typical hospital stay and postpartum recovery period are longer for cesarean delivery than for vaginal delivery. By three months postpartum, however, pain scores after planned cesarean and planned vaginal delivery are similar.

• **Increased maternal morbidity.** Maternal morbidity appears to be higher with planned cesarean delivery than with planned vaginal delivery (8). This includes an increased risk of hysterectomy, wound hematoma, puerperal infection, anesthetic complications and venous thromboembolism. Of note, postpartum sexual function does not appear to be related to method of delivery. Moreover, the available evidence suggests there is no significant difference in maternal mortality for planned cesarean versus planned vaginal delivery.

• **Increased risk of neonatal respiratory problems.** Respiratory distress syndrome and transient tachypnea of the newborn are more common after elective cesarean than after vaginal delivery, and may lengthen the neonate’s hospital stay. Respiratory problems are more frequent after cesarean delivery without labor because mechanisms to reabsorb lung fluid are not fully activated; sometimes such problems occur as a result of iatrogenic prematurity. However, respiratory distress related to prematurity is virtually eliminated if delivery occurs after 39-0/7 weeks of gestation.

• **Increased risk of placenta previa and accreta in future pregnancies.** Placenta previa and accreta are significantly more common in pregnancies following one or more cesarean deliveries. These complications may necessitate cesarean hysterectomy. As such, it may be prudent to avoid elective cesarean delivery in women planning several pregnancies.

• **Increased risk of uterine rupture in future pregnancies.** Most uterine ruptures are related to a trial of labor after a previous cesarean delivery. Uterine rupture may require hysterectomy and is associated with an increased risk of fetal and maternal morbidity and mortality.

• **Complications from multiple abdominal surgeries.** Adhesions increase the difficulty of future intra-abdominal surgical procedures, and may increase the risk of bladder or bowel injury. There does not appear to be a causal relationship between cesarean delivery and subfertility.
RECOMMENDATIONS FOR COUNSELING

On a practical level, I have included below a few comments and suggestions that may help obstetric care providers when faced with a request for CDMR at term.

- Inquire about the motivation for the request. Are there family pressures that should be discussed? Concerns about excessive pain during attempted vaginal delivery should be addressed by providing detailed information about obstetrical analgesia and anesthesia, as well as a possible consultation with an obstetric anesthesiologist. Fear and anxiety stemming from previous childbirth, personal trauma or the experiences of friends and family should also be addressed, if indicated. Providing these women with the best available information about pertinent childbirth issues and appropriate support may alleviate some of their concerns about attempted vaginal birth.

- Review complications of attempted vaginal delivery, such as the possible need for emergency cesarean delivery, fetal risks and the lack of long-term data on perineal injury.

- Clarify the difficulty in comparing the outcome of attempted vaginal versus elective cesarean delivery for both the mother and the fetus.

- Individualize risk estimates according to the primary cesarean rate in your institution and the patient’s a priori risk of intrapartum cesarean delivery. The patient and provider need to take into account patient-specific issues when estimating the risks and benefits of CDMR. Co-morbid medical conditions (e.g., diabetes, hypertension, cardiovascular disease), body mass index (BMI), future reproductive plans, prior childbirth experiences, outcome of previous surgical procedures and the patient’s personal philosophy about childbirth must be considered when choosing the method of delivery.

- Encourage further discussion.

- If you remain ambivalent about proceeding with CDMR, consider consulting your local ethics committee.

- Discuss the ideal timing of delivery. Elective delivery at term should not be scheduled prior to 39-0/7 weeks of gestation. If the American College of Obstetricians and Gynecologists (ACOG) criteria for elective delivery are not met (for example, if the pregnancy is not well dated), consider performing an amniocentesis to confirm fetal lung maturity before proceeding.

- Since risks may change during pregnancy and labor, inform the patient that she can change her plans at any time.

- If the patient elects attempted vaginal delivery, discuss further the possible need for induction of labor, possible need for assisted vaginal delivery and/or intrapartum cesarean delivery, and the risks associated with post-term pregnancy.

- Attempt to remain unbiased at all times. It is most important to avoid paternalism.

SUMMARY

In light of the above data, CDMR can no longer be considered clinically unjustifiable. It now forms part of accepted medical practice. For women considering elective cesarean delivery at term, a thorough discussion of the potential benefits and risks is needed. The best available evidence suggests that planned elective cesarean delivery is associated with a lower risk of postpartum hemorrhage and fetal trauma than is planned vaginal delivery, but it is also associated with a longer hospital stay (slower recovery), an increased risk of short-term neonatal respiratory problems and a greater risk of abnormal placentation and uterine rupture in future pregnancies.
REFERENCES


In the past 30 years the percentage of the American population that is overweight or obese has increased dramatically: 33% are overweight and 34% are obese, with 6% of all adults “extremely” obese. Surgery on patients with a BMI of 50 was once rare. Today it is not uncommon to perform cesarean deliveries or other surgical procedures on women with BMIs of 50 to 70. This epidemic has disproportionately impacted minorities: 49% of African American women are obese, as are 38% of Latinas. Even more alarming: 27% of all children are overweight or obese; thus the problem is likely to be with us for some time (1).

A widespread health issue such as this must have roots in more than just individual behavior and choices. The etiology of obesity is simple math: calories eaten exceed calories expended. Excessive calorie intake is clearly a major factor in obesity but reasons behind this excess must be identified to effect weight loss or the avoidance of excessive gains. Many providers may feel that simply informing a patient of the health risks of obesity, including diabetes, hypertension, coronary heart disease, cancers, joint disease and loss of life expectancy, will change behavior. However, it is clear that “scare tactics” do not work for most patients. Clearly, the influences promoting obesity are powerful and pervasive and can be defined from three perspectives: calorie intake, cost of healthy eating and cultural/community influences (2).

**Calories:** The human species evolved in an environment that provided few calories yet required a significant expenditure of energy to acquire those calories. As a result, our bodies are efficient at utilizing calories and have no limit to storing excessive caloric intake in the form of fat. Certain foods require more of a metabolic cost to convert food to body fat. Complex carbohydrates can require 25% of their calories for metabolism in contrast to fats, which only require 3%. For women, this may have been beneficial since they would, in times of plenty, store extra nutrients needed to subsequently nourish a developing fetus or breastfeed a newborn. Today, few calories need to be expended to acquire large amounts of calorie-dense food. Food portions have increased dramatically at restaurants with greater emphasis on fatty foods (fried or buttered) and sweetened drinks (soft drinks and juices with increased portion sizes). This makes it easy for a person to consume over 1,000 calories in a single meal.

Many of our weight loss efforts have been related to decreasing caloric intake through dieting. There are numerous diet strategies including low fat (Ornish), moderate fat (glycemic index or balanced reduction such as Weight Watchers or Jenny Craig) and high protein (Atkins or South Beach). Different patients have different degrees of success with different approaches. Studies that compare diets find that the single most important factor predicting success is the patient’s compliance with the diet (3). For this reason there is no perfect dietary strategy. Patients should choose an approach that emphasizes foods they like, which may increase compliance for a longer period of time. Most diet plans stress reduced/different caloric intake as a lifestyle change and not as a punishment that must be endured until one becomes “skinny.” The provider needs to stress the concept of “healthy weight,” not fashionable weight. No matter what diet plan is followed, the loss of 10% of body weight will positively impact co-morbidities of hypertension, diabetes and sleep apnea.

Just as hunting and gathering in a calorie-scarce environment controlled weight in early humans, an increase in physical activity helps weight loss by increasing the expenditure of calories in modern humans. Most patients do not increase physical activity levels enough to truly generate significant weight loss. However, it is still impor-
tant for the physician to encourage patients to participate in physical activity such as walking for 30 minutes each day to help with conditioning and muscle tone. Again, our goal should be healthy, not “skinny.”

**Cost/Commerce:** Over the past 30 years there has been a major shift in the cost of certain foods. “Healthy” foods cost more than “fast” foods, in part due to federal subsidies for most grain products, which are used to make corn syrup for sweeteners, bakery goods and other highly processed foods. Foods such as sweetened cereal, chips and cookies have a longer shelf life and are commonly stocked in “quick marts.” Rarely do these vendors carry fresh fruits and vegetables. Full-service grocery stores are seldom found in rural areas or inner cities since they have very slim operating margins and are not profitable in these settings. As a result many individuals, especially lower socioeconomic families, have trouble easily obtaining healthy foods (4). Instead, they have ready access to “fast” food where one can get a complete meal with over 1100 calories for less than five dollars. “Super size” portions offer even more calories at a low cost. Even the Women, Infants and Children (WIC) program and food banks typically provide surplus foods with high fat and caloric content.

**Culture/Community:** Culture exerts a powerful influence on health and weight, with cultural norms transmitted through people that a person socializes with or through members of one’s extended family or community. These groups have considerable influence on an individual’s value system and accepted norms. If two-thirds of the American population are either overweight or obese, this becomes the cultural norm (5). In some groups, including many Native American tribal groups, a fat baby is a healthy baby. Many older members of these communities remember how, only a few decades ago, children died of malnutrition. As children become larger, expectations for “ideal weight” by the tribe also increase. In this way social norms regarding obesity alter individual perceptions. Cultural relaxation of standards of personal discipline and lack of support for healthy lifestyle choices contribute to this rapid national increase in obesity. For many groups food is central to community/family functions and failure to eat large amounts of food is considered rude and antisocial.

**Summary:** So how do we approach this epidemic? Prevention, of course, is best. But for those patients who need treatment, we must address all three aspects of the problem. Individuals need to be educated concerning health problems caused by their obesity, including the role of calories, too little activity and lack of reasonable goals for weight loss. A recommendation of a loss of 10% of body weight is achievable and results in improved health. Physicians should emphasize that the goal of weight loss is better health and not to fit into a size 6 dress. Patients should be taught that a change in nutritional behavior improves health and is not a punishment for a lack of self-control. The dietary strategy a patient chooses is not as critical as the ability for the patient to remain compliant with the dietary modification.

Governmental agencies need to make healthier foods, including fresh fruits and vegetables, more accessible and affordable through subsidies and then distributed through state and federal programs. Some health proponents have promoted the idea of taxing sweetened soft drinks: the so-called Fat Tax. Heightened tax rates have helped to decrease the consumption of cigarettes. Because soft drinks and fast foods are major sources of excessive calories with little nutritional value, the Fat Tax may have some support among those who believe behavioral change can be achieved through taxation and penalties.

Finally, a patient’s community needs to support an individual’s decision to lose weight. Many patients are sabotaged by their immediate family, co-workers and other members of their community. Rather than support an individual’s decision to modify behavior, members of a person’s social network often provide calorie-laden foods, insist on eating at restaurants with limited healthy choices, and refuse to support the individual when he or she tries to free up time to exercise. Community leadership needs to provide safe
areas to walk or exercise, support farmer’s markets or grocery stores, and encourage healthy choices that are consistent with cultural roots.

Obesity is a national epidemic that is occurring due to economic and cultural pressures that make high-calorie foods readily available and culturally acceptable, a shifting national norm of what is an acceptable weight, and decreased emphasis by individuals and the greater community on healthy life choices. Diets and weight loss pills are not the answer. Prevention is the key. For individuals who are already obese, the health care system needs to provide motivational counseling, nutritional education and family counseling. The most effective motivation continues to be that of improved health and better quality of life, not some external expectation that cannot be achieved by most of the population.
REFERENCES:


OBJECTIVE

Abnormal umbilical artery Doppler velocimetry (UADV) is associated with adverse pregnancy outcomes and is now commonly used to assist in the timing of delivery in high-risk pregnancies. However, existing studies have been criticized because of their failure to include appropriate control groups and, as such, their inability to adequately account for differences in gestational age. This is significant because measures of adverse pregnancy outcomes are gestational-age dependent with more complications seen in infants born at earlier gestational ages. The current study is designed to address this issue by comparing perinatal outcome in fetuses with abnormal UADV with the ideal control group – namely, their normal co-twins. The primary perinatal outcome measures are intrauterine fetal demise (IUFD), neonatal demise (NND), oligohydramnios (maximal vertical pocket <2 cm), intrauterine growth restriction (defined as <10% percentile [IUGR]), very low birth weight (VLBW) (<1500g), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and sepsis.

METHODS

All twin pregnancies that had UADV performed at Yale-New Haven Hospital at greater than 24 weeks’ gestation from June 1998 to June 2007 were identified using an established perinatal database (n=275). Inclusion criteria were twin pregnancies undergoing UADV with either mildly or severely discordant Dopplers. Mildly abnormal Dopplers were defined as umbilical artery Dopplers with elevated systolic/diastolic (S/D) ratios. Severely abnormal Dopplers included those with absent or reversed end-diastolic flow. Those patients for whom neonatal outcomes were unable to be evaluated (patients who ultimately delivered at outside hospitals or those who underwent selective reduction) were excluded from the study. Using a matched twin cohort analysis in pregnancies with discordant UADV, perinatal outcome was compared between fetuses with abnormal UADV and their normal co-twins (including IUFD, NND, oligohydramnios, IUGR, VLBW, RDS, IVH, NEC, BPD and sepsis). Statistical analysis was performed using chi-square and logistic regression modeling (p<0.05 defined as statistical significance). Data were also analyzed by chorionicity of the twin pregnancies.

RESULTS

Fifty-four twin pairs met inclusion criteria. Oligohydramnios (22.2% vs. 5.6%; p=0.012), IUGR (66.7% vs. 5.6%; p<0.001) and VLBW (54.0% vs. 25.5%; p=0.003) were more frequent in twins with abnormal UADV than in their normal co-twins, respectively. These associations were stronger in the 24 twin pairs with severely abnormal discordant UADV (absent or reversed flow in one twin) compared with the 30 twin pairs with mildly abnormal discordant UADV (elevated S/D ratio in one twin).

Composite perinatal outcome (IUFD, NND, RDS, IVH, NEC, BPD and/or sepsis) was not significantly different in fetuses with abnormal UADV compared with their co-twins (48.2% vs. 53.7%, respectively; p=0.56). Interestingly, abnormal UADV was more common in the non-presenting twin (70%; p<0.0001; OR 5.6 [95% CI, 2.3-14.1]).
CONCLUSIONS

Using a matched twin cohort study design that controls for gestational age and maternal co-morbid conditions, this study confirms that abnormal UADV is associated with IUGR, VLBW and oligohydramnios, but not with other short-term adverse pregnancy outcomes. Early delivery (mean GA 32.9 weeks) due to the compromised twin may explain the high perinatal morbidity in both groups. The observation that abnormal UADV is more common in non-presenting twins suggests that the relative health of the twins may affect which twin presents.
Altered Proteoglycan Homeostasis in Uterosacral Ligaments of Women with Prolapse

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OBJECTIVES

Currently, proteoglycan metabolism is poorly understood in the uterosacral ligaments (USLs), which are key structures of the pelvic support system in women. Aggrecan is a large multidomain proteoglycan protein in the extracellular matrix (ECM) that co-localizes with collagen and assists in its organization and stability, thereby contributing to the tensile strength, compliance and resistance of tissues. Previously, we have confirmed expression of a known developmental aggrecanase, ADAMTS1 (a disintegrin and metalloproteinase with thrombospondin-1 motifs), in adult human USLs and found it to be deficient in women with pelvic organ prolapse (POP). The objective of this study was to determine if alterations of aggrecan exist in the USLs of women with POP and to determine if ADAMTS1 regulates aggrecan catabolism in USL cells.

RESULTS

Seventeen women with normal support and 14 women with stage II or greater POP were included. There were no differences between the two groups regarding parity or menopause; however, the POP group was significantly older than the control group (p=0.01). Expression of ADAMTS1 was decreased in USL specimens from women with POP compared to controls (p=0.04). Conversely, aggrecan was increased in POP specimens (p=0.02). Constitutive expression of ADAMTS1 resulted in a twofold decrease in aggrecan mRNA expression (p<0.05) and an increase of aggrecan protein catabolites consistent with cleavage at the aggrecanase cleavage site within the aggrecan interglobular domain.

CONCLUSIONS

There is altered expression of the proteoglycan aggrecan and decreased expression of ADAMTS1 in the USLs of women with POP. ADAMTS1 cleaves the substrate aggrecan in USL cells in vitro. Dysregulation of aggrecan homeostasis involving ADAMTS1 may affect the integrity of the USLs in women with POP. Further investigation of the role of ADAMTS1 and aggrecan in the ECM of the female pelvic support system may aid in the development of new treatment strategies for women with POP.
The Effects of Estrogen on Peripheral HOXA10 Expression

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OBJECTIVE

HOXA10 influences body axis patterning during embryogenesis. It is also essential to maintaining developmental plasticity within adult tissue, namely the female reproductive tract and the hematopoietic system. Many studies have elucidated the mechanisms behind HOX's gene regulatory effects in uterine tissue. In addition, it has been shown that estradiol enhances HOXA10 expression within the endometrium. Less is known regarding serum regulators of HOX expression. In this study, we culture lymphocytes with estradiol and quantify resultant HOXA10 expression.

METHODS

U937 cells, derived from a histiocytic lymphoma and serving as an in vitro model for serum monocytes, were cultured with graded concentrations of estradiol. After 12 hours of steroid exposure, RNA extraction was performed, followed by absorption spectrometry for RNA quantification. HOXA10 expression was determined via RT-PCR.

RESULTS

Estradiol suppressed lymphocytic HOXA10 expression. This suppression was not dose dependent. The addition of progesterone did not result in further HOXA10 expression suppression or enhancement.

CONCLUSIONS

HOXA10 plays a vital role in body axis patterning during embryogenesis. In adult tissue, it allows for continued developmental plasticity. In physiological doses, estradiol and progesterone up-regulate endometrial HOXA10 expression. In our study we have demonstrated that sex steroids do not have a similar effect on peripheral HOXA10 expression. Conversely, expression is suppressed in a non-dose-dependent manner.
Ovarian Preservation and Staging in Reproductive-Age Endometrial Cancer Patients

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OBJECTIVES

The goal of this case review was to evaluate the influence of complete surgical versus clinical staging, including the impact of ovarian preservation, on the outcome of young patients with endometrial carcinoma.

METHODS

A retrospective chart review was performed on all patients with endometrial cancer diagnosed at age 45 years or younger from 1960 until 2006 who were treated at Yale-New Haven Hospital (YNHH). There were 251 patients included in the study. Clinical, epidemiological and histological data were extracted. Histological slides were reviewed by the gynecologic pathologist. Statistical analysis was performed, and p<0.05 was considered statistically significant.

RESULTS

More than half of the patients underwent surgical staging. A bilateral salpingo-oophorectomy (BSO) was part of the surgery in most cases. Fewer than 5% of patients were diagnosed with recurrence. In patients with grade 1 disease, surgically staged patients had a significantly longer overall survival (p=0.003). Patients who underwent a BSO had a trend toward longer disease-free survival. Stage I disease patients who underwent BSO had significantly longer disease-free survival (p=0.013).

CONCLUSIONS

BSO seems to lead to better disease-free survival in young endometrial cancer patients, especially those with stage I disease, but not to improved overall survival. In the absence of risk factors, a more conservative approach to surgical staging may be possible in young women with early-stage low-grade endometrial cancer but BSO should be strongly considered as part of the surgical treatment.
In most metazoa, oocytes become arrested at the prophase of the first meiotic division. This arrest may last from a few years in *Xenopus* to several decades in humans, and it is characterized by synthesis and storage of dormant mRNAs. The resumption of meiosis marks the onset of oocyte maturation and is associated with suppression of transcription, which persists until zygotic genome activation (ZGA). Consequently, gene expression during oocyte maturation, fertilization and early embryogenesis depends on translational activation of maternally derived mRNAs stored in the oocyte during the first meiotic arrest.

The best-characterized mechanism for regulating translational activation during early development is via cytoplasmic polyadenylation and involves a complex of RNA-binding proteins that interact with the 3’ untranslated region (3’ UTR) of the stored mRNAs. Embryonic poly-A binding protein (ePAB), identified in *Xenopus* oocytes, is the predominant poly-A binding protein expressed during early *Xenopus* development. ePAB plays a central role in the translational regulation of maternally derived transcripts during a critical period of early development when transcription from the zygotic genome is suppressed. ePAB, along with a complex of proteins, binds to and stabilizes maternal mRNAs, presumably preventing degradation and, when appropriate, promoting their translation.

Mouse and human homologues of ePABs have been identified and demonstrate an expression pattern similar to that of Xenopus ePAB. Based on the conserved homology and the similar pattern of expression between these species, we hypothesized that ePAB may play a key role in regulating expression of maternally derived mRNA transcripts during early mammalian development.

To test this hypothesis, we generated ePAB-null mice by targeted deletion of ePAB exon 2, which resulted in a translational frameshift mutation and consequently a premature stop codon. Here we describe construction of the ePAB targeting vector and generation of the ePAB-null mutant mice. Interestingly, male and female ePAB−/− mice were viable and appeared phenotypically normal. However, ePAB−/− female mice were infertile, while ePAB−/− males and ePAB+/− of both sexes demonstrated normal fertility. Additional studies to characterize the molecular pathophysiology of the fertility defect remain ongoing.
OBJECTIVES

Homebox genes are transcriptional regulators that orchestrate embryonic development. The HOXA13 gene is responsible for the development of the vagina and regulates extracellular matrix constituents. We hypothesized that vaginal expression of HOXA13 may be decreased in women with pelvic organ prolapse (POP) and sought to determine if hypoestrogenism affects its expression.

METHODS

Biopsy specimens were obtained from the anterior apex of the vagina from women with and without POP. Immunohistochemistry and real-time polymerase chain reaction were used to determine HOXA13 expression in premenopausal controls, in premenopausal women receiving leuprolide acetate, and in premenopausal and postmenopausal women with POP.

RESULTS

HOXA13 was expressed in all specimens. HOXA13 expression was 14-fold lower in premenopausal women with prolapse than in premenopausal controls (p<0.001). In both POP groups, HOXA13 expression was lower than in the leuprolide group (p<=0.001). There were no differences in HOXA13 expression between premenopausal controls and women treated with leuprolide acetate (p=1.0) or between the premenopausal and postmenopausal POP groups (p=1.0).

CONCLUSIONS

Vaginal HOXA13 expression is diminished in women with POP compared to women with normal support. In women with POP, expression of HOXA13 was not affected by menopause. Expression of HOXA13 was also not affected by exposure to leuprolide acetate, suggesting that estrogen and HOXA13 work through separate pathways in the extracellular matrix metabolism of the vagina. Understanding genetic predispositions to developing POP may identify younger patients at risk who may benefit from preventive strategies such as weight loss or smoking cessation and not necessarily from estrogen therapy.

PUBLICATION

ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the Society for Maternal-Fetal Medicine 2010 Annual Meeting, February 1-6, Chicago, IL

ORAL PRESENTATIONS


POSTER PRESENTATIONS


Role of Diabetes and BMI in Determining Baroreceptor Sensitivity. K. Williams, F. Galerneau, L. Elgart.


Abstracts from Recent Scientific Meetings


Interleukin-6 Trans-Signaling Molecules Soluble GP130 and Soluble IL-6 Receptor in the Amniotic Fluid (AF) of Women with Intra-Amniotic Inflammation (IAI) and Preterm Premature Rupture of Membranes (PPROM). S. Lee, I.A. Buhimschi, G. Zhao, A.T. Delay, M.O. Bahtiyar, C. Han, C.S. Buhimschi.


Role of Preeclampsia and BMI in Determining Baroreceptor Sensitivity. K. Williams, F. Galerneau, L. Elgart.


* This work received the Research Excellence Award, Society for Maternal-Fetal Medicine, 2010 – Plenary Session I
ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Poster Presentation at the Society of Gynecologic Oncologists 41st Annual Meeting on Women’s Cancer™, March 14-17, 2010, San Francisco, CA

POSTER PRESENTATION

ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the American Urogynecologic Society 2009 Annual Meeting, September 24-26, Hollywood, FL

ORAL PRESENTATIONS


ORAL POSTER PRESENTATION


POSTER PRESENTATION

ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the American Society for Reproductive Medicine 2009 Annual Meeting, October 17-21, Atlanta, GA

ORAL PRESENTATIONS


Tissue Selective Estrogen Complexes (TSECs) Modulate Markers of Proliferation in Uterine and Breast Cancer Cells. J. Kulak, B. Komm, H.S. Taylor.


Reproductive Hormone Dynamics Identify Distinctions Between Diminished Ovarian Reserve (DOR) and Chronological Aging. K. Zhang, G. Zeitlian, N. Santoro, L. Pal.


POSTER PRESENTATIONS

Viability Scores Determined by Metabolomic Assessment of Embryo Culture Media Correlate with IVF Outcome in Women Undergoing Single Embryo Transfer on Day 2: A Prospective Multi-Center Study. E. Seli, L. Botros, M. Henson, P. Roos, D. Sakkas, Metabolomics Study Group.


ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Poster Presentations at the Society for Gynecologic Investigation 2010 Annual Meeting, March 24-27, 2010, Orlando, FL

ORAL PRESENTATIONS


Differentiation of Uterine Stem Cells into Pancreatic Beta Cells. X. Santamaria, E. Massasa, Y. Feng, H.S. Taylor.

Bazedoxifene Treatment Causes Regression of Endometriosis in a Mouse Model. J. Kulak, B. Komm, H.S. Taylor.

Effect of In-Utero Cellular Telephone Radiation Exposure on Reproductive Performance of Mice. L.N. Odom, T.S. Aldad, H.S. Taylor.


POSTER PRESENTATIONS


Effects of Cigarette Smoke on Recruitment of Bone-Marrow-Derived Stem Cells to the Uterus. Y. Zhou, E.M. Jorgensen, H.S. Taylor.

G-CSF Inhibits Migration of Bone Marrow-Derived Stem Cells to Endometrium. H. Du, H. Naqvi, H.S. Taylor.


Umbilical Artery (UA) Doppler Velocimetry in Fetuses Delivered by Women with Intraamniotic Inflammation (IAI), Histologic Chorioamnionitis (HCA) and Funisitis. K.H. Campbell, E.F. Werner, H. Azpurua, I.A. Buhimschi, C.S. Han, J.A. Copel, M.O. Bahtiyar, A.T. Dulay, C.S. Buhimschi.


CCL5 Is the Major First Trimester Decidual Cell-Secreted Chemokine for Dendritic Cell Recruitment in Response to Pro-Inflammatory Stimuli. M. Li, H. Yang, L.M. Coraluzzi, M. Rahman, S.J. Huang.

Epithelial-Mesenchymal Transition Generates Cancer Stem Cells with Metastatic Potential. G. Yin, V. Craveiro, J. Holmberg, H.-H. Fu, A. Alvero, G. Mor.


Viability Scores Determined by Metabolomic Assessment of Embryo Culture Media Correlate with IVF Outcome in Women Undergoing Single Embryo Transfer on Day 2: A Prospective Multi-Center Study. E. Seli, L. Botros, M. Henson, P. Roos, D. Sakkas, Metabolomics Study Group.


Decreased Expression of Placental Leukocyte Immunoglobulin-Like Receptors (LILRs) in Preeclampsia (PE) and Intrauterine Growth Restriction (IUGR): Implications for Immune Privilege. S. Guller, Z. Tang, T. Niven-Fairchild, S.J. Huang, C.S. Buhimschi, I.A. Buhimschi.


THE YEAR IN REVIEW

Welcome to Our New Ob/Gyn Interns

We are pleased to announce the results of the 2009 National Ob/Gyn Residency Match Program. We received a record 418 applications. Of the 89 candidates we invited to interview, 73 accepted. We have matched six outstanding, highly accomplished physicians.

DARRAH DOYLE, MD – University of Massachusetts Medical School

Darrah received her BA (Art History) at Northwestern University. She was the recipient of numerous awards including the Weinberg Undergraduate Research Award, Melville J. Herskovitz Library of African Studies Research Award and Carson J. Webster Prize for distinguished honors thesis, Northwestern University Department of Art History. Darrah has been actively involved in a number of community activities at UMASS, including Student Chapter Co-Leader for Physicians for Human Rights. Her research project in provider advice regarding pregnancy-associated obesity and gestational weight gain has inspired a commitment to a research agenda that has the potential to affect both mothers and their offspring. Darrah’s hobbies and interests include golf, running and learning about the history of art and medicine. She was a member of the Haydenettes Synchronized Figure Skating Team and won the US National Championships in 2000 and 2001.

SAMI MAKAROUN, MD – University of Pittsburgh School of Medicine

Sami received his BA (Biology) at the University of Chicago. He has been actively involved in numerous research projects: (i) a retrospective study to assess the long-term PSA outcomes and adverse events of prostate brachytherapy for the treatment of clinically localized prostate cancer; (ii) performed and fine-tuned molecular biologic research assays and provided creative input and direction on a microarray project intended to uncover the molecular mechanisms underlying the slowing of physiologic growth with increasing age; (iii) to determine optimal culture conditions allowing differentiation of human embryonic stem cells into insulin-producing pancreatic beta cells and dendritic cells for transplant and immune tolerance, respectively, for treatment of children with type 1 diabetes. Sami has also been involved in a number of community activities at the University of Pittsburgh. He is intermediately fluent in French. Among his hobbies and interests he lists reading, writing, playing the piano, cooking and acting in plays/skits.
ANTONIO MALDONADO, MD – University of Texas Southwestern Medical School at Dallas

Antonio received his BS (Biology) at Yale University. He has been avidly involved in several educational programs at UT Southwestern, including: (i) group leader for the Health Professions Recruitment and Exposure Program, which is a six-week program for high school students interested in science and medicine; (ii) Organizer/Student Panel member of the 2007 UT Southwestern Pre-medical Conference; (iii) mentor for the UT Southwestern Mentoring Program to local underprivileged middle school students; (iv) member and co-vice president of the National Network of Latin American Medical Students (NNLAMS), meant to support the advancement of Latin American individuals in medical school. In 2008 UT Southwestern was selected as a top medical school for Hispanic students by Hispanic Magazine. Antonio, along with two other students, was selected to represent UT Southwestern in a photo for the cover of the magazine. Selection was based on academic performance, leadership and community service. He is fluent in Spanish, both reading and writing. His hobbies and interests include playing the guitar, reading suspense novels and spending time with friends. He also enjoys participating in sports, including basketball, soccer and softball.

NATU MMBAGA, MD – Meharry Medical College School of Medicine

Natu received her BS (Biology) from Middle Tennessee State University. She has been the recipient of numerous awards including the American College of Obstetricians and Gynecologists Gibbons Award at the 2007 annual District VII Meeting. Natu has been actively involved in numerous academic and community projects, including: (i) President of the Henry W. Foster Ob/Gyn Interest Group, which conducts monthly meetings with students interested in Ob/Gyn; (ii) Community Service Chair for the AOA Medical Society; (iii) Team Captain of the Meharry Medical College March of Dimes Fundraiser; (iv) AIDS Advocacy Network Steering Committee member to help mobilize the American Medical Student Association’s local chapters to increase HIV and global health awareness campaigns. Among Natu’s hobbies and interests are movies, hiking, traveling, rock climbing and dining with friends and family.

MARK SILVESTRI, MD – University of Chicago Pritzker School of Medicine

Mark received his BA (Government) from Harvard University. He has received several awards including the Dean’s Promise Scholarship, University of Chicago Pritzker School of Medicine, 2005-2009, a four-year full-tuition scholarship for academic achievement. Mark has been actively involved in teaching programs at the University of Chicago Pritzker, including: (i) Medical Ethics Teaching Assistant; (ii) Physical Diagnosis Teaching Assistant; (iii) Clinical Skills Teaching Assistant; (iv) Human Morphology Teaching Assistant. He has also been involved in community programs, including: (i) Pritzker Security Task Force; (ii) Music Leader, Treasurer, Immanuel Anglican Fellowship; (iii) President, Pritzker Christian Fellowship; (iv) Volunteer for the Adolescent Substance Abuse Program. He participated in an NIH-sponsored Pritzker Summer Research Program that involved collecting and analyzing demographic, perioperative, functional and quality-of-life data for all ulcerative colitis patients who have undergone ileal pouch surgery with the new laparoscopic approach. Mark’s hobbies and interests include guitar, photography and running.
LISA ZUCKERWISE, MD – Albert Einstein College of Medicine/Yeshiva University

Lisa received her BS (Human Biology, Health and Society) from Cornell University. She was the recipient of the New York State Higher Education Services Corporation Scholarship for Academic Excellence (2001-2004). Lisa has been actively involved in numerous academic activities while at Albert Einstein, including: (i) Peer Tutor for first- and second-year medical students in histology, biochemistry, endocrinology, cardiovascular, renal, pulmonary and neurology courses; (ii) Co-Front Desk Lead and Clinical Teams Leader, Einstein Community Health Outreach, coordinating a variety of medical services to uninsured patients; (iii) American Medical Women’s Association; Co-Chair of Albert Einstein College of Medicine chapter. Her research project involves a retrospective chart review with the goal of determining the clinical utility of CA125 and CA19-9 measurements in patients with uterine papillary serous carcinoma. Lisa’s hobby is scuba diving.
Our Fellowship Graduates and Their Next Destinations

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

Eric Hodgson, MD
Faculty of Yale University – Maternal-Fetal Medicine

Mark Wehrum, MD
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology,
Womack Army Medical Center, Fort Bragg, NC

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

Elena Ratner, MD
Faculty of Yale University – Gynecologic Oncology

Our Residency Program Graduates and Their Next Destinations

Eve Bernstein, MD
Maternal-Fetal Medicine Fellowship – University of Washington

Leo Doherty, MD
Reproductive Endocrinology & Infertility Fellowship – Yale University

Christina Duzyj, MD
Maternal-Fetal Medicine Fellowship – Yale University

Sara Isani, MD
Gynecologic Oncology Fellowship – Albert Einstein College of Medicine

Michael Reel, MD
Private Practice – Obstetrics, Gynecology & Menopause Physicians

Joyce Varughese, MD
Gynecologic Oncology Fellowship – Yale University

Erica Wang, MD (2008 Graduate, Residency Program)
Reproductive Endocrinology & Infertility Fellowship – University of California, San Francisco
Newest Additions to the Yale Faculty

Sonya S. Abdel-Razeq, MD, joined the faculty of the Section of Maternal-Fetal Medicine in September. After graduating summa cum laude from St. John’s University, she attended SUNY Buffalo School of Medicine, receiving the Clyde B. Randall Award for best thesis in obstetrics and gynecology. She remained there for her Ob/Gyn residency, earning the Robert J. Patterson Memorial Award for Patient Care.

Dr. Abdel-Razeq came to Yale as a Maternal-Fetal Medicine fellow and then entered Yale’s fellowship in Surgical Critical Care and Surgical Emergencies. Her research interests include fetal inflammation and evaluation and prognosis of renal disease in the critically ill.

Antonette Dulay, MD, joined the faculty of the Section of Maternal-Fetal Medicine in July. She graduated magna cum laude from Barnard College in 1998, earning her MD from NYU School of Medicine and remaining there for her Ob/Gyn residency. She received multiple teaching awards and the NYU Shenker Award for best resident research.

Dr. Dulay became a Yale Maternal-Fetal Medicine fellow in 2006, publishing 18 research articles, chapters and reviews, two of which she presented at the Society for Maternal-Fetal Medicine’s Annual Meeting. During her third fellowship year, she received the SMFM/AAOGF Scholarship Award, securing funding for three years of research training.

Elisabeth A. Erekson, MD, MPH, joined the Section of Urogynecology and Reconstructive Pelvic Surgery as Assistant Professor in August 2009. She attended the University of Illinois School of Medicine and served her residency at Saint Louis University School of Medicine. She completed a fellowship in Female Pelvic Medicine & Reconstructive Surgery at Women and Infants Hospital/Brown University, concurrently earning a Master of Public Health (MPH).

Dr. Erekson’s clinical interests include robotic surgery and other minimally invasive surgical treatments for correction of prolapse and urinary incontinence. She is actively researching the relationship between pelvic organ prolapse and obstructive bowel symptoms.
PHOTO HIGHLIGHTS FROM THE YOGS REUNION IN NEW HAVEN, APRIL 2009
PHOTO HIGHLIGHTS FROM THE YOGS REUNION IN NEW HAVEN, APRIL 2009
PHOTO HIGHLIGHTS FROM THE 2009 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
PHOTO HIGHLIGHTS FROM THE 2009 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
**HONORING ALAN DECHERNEY**

On April 17, 2010, we will hold our third annual Yale Obstetrical and Gynecological Society Alumni Reunion Event in honor of Dr. Alan DeCherney’s long and illustrious career. Alan is currently Head of the Program in Reproductive and Adult Endocrinology and Chief of the Reproductive Biology and Medicine Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health.

Several of Alan’s many colleagues will be on hand to help us celebrate Alan’s career as it touched theirs. Richard Berkowitz and Peter Schwartz, who worked with Alan at Yale in their early days, will elaborate on the relationship of the maternal-fetal medicine and gynecologic oncology worlds with reproductive endocrinology. And two of Alan’s most renowned disciples, Hugh Taylor and David Frankfurter, will share the impact that Alan’s training has had on their work in infertility.

Alan’s career has spanned from his training days at Penn through chairmanships at Tufts and UCLA to his present position at the NIH, but he has always considered his years at Yale among his most rewarding. He arrived in New Haven in 1975 to share an assignment with last year’s honoree, Don Coustan: to teach our residents how to care for patients, using the British Firm system. He also promoted the growth of our Reproductive Endocrinology section, later becoming the John Slade Ely Professor of Obstetrics and Gynecology and official division director.

Somehow, Alan also found the time to serve as Editor-in-Chief of *Fertility & Sterility*, and is one of the very few Ob/Gyns ever to be on the editorial board of the *New England Journal of Medicine*. He has also been the subject of a multiple-article series in the *New Yorker*, as well as a much trusted and frequently quoted source to the *New York Times*.

We would like to thank Alan for his continued devotion to Yale. Despite spending only 17 years here full-time, he has always remained available to all of us for consults, education and entertainment. We hope that his colleagues and trainees, whose lives he continues to influence, will come back to honor Alan, learn something new and be well entertained.

**IN FOND MEMORY**

Over the past year, we have lost a number of colleagues who played an integral role in influencing our personal and professional lives.

**Noel McCarthy, MD**

Noel McCarthy, MD, MPH, FACOG, passed away on July 22, 2009. As the guiding power behind the New England Obstetrical and Gynecological Society, he was a vibrant and vital force in our specialty regionally. Dr. McCarthy was also honored by ACOG in 2008 with the Outstanding District Service Award for his work advancing the education of members and medical students, residents and fellows who attend ACOG meetings. Universally loved and respected, nearly every Ob/Gyn in New England can claim Dr. McCarthy as a friend – and he reciprocated by being a true and loyal colleague.
Samuel S. Thatcher

Samuel S. Thatcher, MD, PhD, passed away on December 18, 2009 in Tennessee. Dr. Thatcher began his career in reproductive science in 1973 studying the detrimental effects of aging on reproduction, culminating in a PhD in human anatomy/reproductive biology at West Virginia University where he simultaneously received his MD in 1981. He completed his residency training in obstetrics and gynecology and a fellowship in reproductive endocrinology at Yale-New Haven Hospital, later serving on the faculty in the Division of Reproductive Endocrinology at Yale before returning to East Tennessee in 1988. He was director of reproductive endocrinology at the ETSU Department of Obstetrics and Gynecology until 1995 when he opened a private practice. Dr. Thatcher received numerous teaching and lecture awards and authored one of the first comprehensive books on polycystic ovary syndrome. He was an editorial reviewer for several professional publications and enjoyed writing and speaking on fertility issues on the local, national and international levels.

Albert Diddle, MD

Albert W. Diddle, MD, one of the original researchers on oral contraceptives and a graduate of Yale Medical School, passed away December 23, 2009 at age 100. He was the first Board-Certified Ob/Gyn in Knoxville, Tennessee, and chaired the Ob/Gyn Residency program at the University of Tennessee Medical Center.

Malcolm Brochin, MD

Malcolm Brochin, MD, a member of Yale’s Department of Obstetrics & Gynecology for over 26 years, passed away on November 5, 2009. In addition to his affiliation with Yale-New Haven Hospital, Dr. Brochin had a private practice on Sherman Avenue in New Haven.

John R. Lyddy, MD

John R. Lyddy MD, 90, passed away on October 3, 2009. Dr. Lyddy first practiced general medicine in Bridgeport, then came to Yale where he completed his residency in Ob/Gyn in 1957. A World War II veteran, he served at Bridgeport Hospital both as Ob/Gyn Department Chair and Chief of Staff.

H. David Kearing, MD

H. David Kearing, MD, 68, died on September 9, 2009 at his home in Brackney, Pennsylavania. After receiving his medical degree from Cornell, Kearing completed a residency in Ob/Gyn at Yale. He practiced Ob/Gyn in Binghamton, NY, until his retirement in 2001.

BIRTH ANNOUNCEMENTS

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

Cade Henry Wehrum – 8 pounds, 7 ounces – June 8, 2009 (Mark Wehrum, DO and Dawn)

Gabriella Renee Silasi – 5 pounds, 15 ounces – July 15, 2009 (Dan-Arin Silasi, MD and Michelle)
Connor David Doherty – 7 pounds, 3 ounces – August 8, 2009 (Leo Doherty, MD and Michelle)

Matteo Davide Santin – 8 pounds, 11 ounces – August 13, 2009 (Stefania Bellone, PhD and Alessandro Santin, MD)

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

GRANTS AWARDED

Dr. Gil G. Mor – P01 National Institute of Child Health & Human Development (NICHD) – “Function of Toll-like Receptors Throughout Gestation.”

Dr. Ilana Chefetz-Menaker – Life Sciences Research Foundation – “Identification and Characterization of Ovarian Cancer Stem Cells.”


Dr. Jessica L. Illuzzi – National Institute of Allergy and Infectious Diseases (NIAID) – Duration of Intrapartum Antibiotic Prophylaxis for Group B Streptococcus.”

Dr. Hugh S. Taylor – The John B. Pierce Laboratory Inc. – “Compromised Microcirculation in Women with Polycystic Ovary Syndrome.”

Dr. Seth M. Guller – R01 National Institute of Child Health & Human Development (NICHD) – “Targeting Placental Pathophysiology in IUGR and Preeclampsia.”

Dr. Charles J. Lockwood – National Institute of Child Health & Human Development (NICHD) – Women’s Reproductive Health Research Career Development Program (K12).

Dr. Vikki M. Abrahams – Burroughs Wellcome Fund – “The Role of Placental Nod-Like Receptors in Infection-Associated Preterm Labor.”

Dr. Heidi Wen Chen – American Urogynecologic Society Grant – “Using Quantitative Sensory Testing of the Sensory Distribution of the Pudendal Nerve in Predicting Success of Sacral Neuromodulation.”

Dr. Antonette Dulay – American Board of Obstetrics and Gynecology/American Association of Obstetricians & Gynecologists Foundation (ABOG/AAOGF) Award – “A Role for Soluble Modulators of Innate Immunity in Regulating the Intra-amniotic Inflammatory Response to Infection.”

Dr. Yingqun Huang – State of Connecticut Department of Public Health – “Molecular Function of Lin28 in Human Embryonic Stem Cells.”
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 (90.0)
- Yale Maternal-Fetal Medicine (90.8)
- Yale Gynecologic Oncology (87.2)
- Yale Fertility Center (91.3)

YALE OB/GYN PHYSICIANS ON TOP DOCS LISTS

In New York Magazine’s 12th annual “Best Doctors” issue, five physicians from Yale’s Department of Obstetrics, Gynecology and Reproductive Sciences were recognized:

- Masoud Azodi, MD (Gyn Oncology)
- Joshua Copel, MD (MFM)
- Michael Paidas, MD (MFM)
- Pasquale Patrizio, MD (REI)
- Hugh Taylor, MD (REI)

Closer to home, Connecticut Magazine identified eight of our physicians as “Top Docs” in their 2009 annual survey:

- Joshua Copel (MFM)
- Edmund Funai (MFM)
- Charles J. Lockwood (MFM)
- Urania Magriples (MFM)
- Pasquale Patrizio (REI)
- Hugh S. Taylor (REI)
- Thomas J. Rutherford (Gyn Oncology)
- Peter E. Schwartz (Gyn Oncology)
**U.S. NEWS & WORLD REPORT NAMES YNHH ONE OF THE NATION’S TOP HOSPITALS**

In its August 2009 issue, *U.S. News & World Report* named Yale-New Haven Hospital one of “America’s Best Hospitals” for the third straight year – the only Connecticut hospital and one of only three hospitals in New England to claim this distinction.

YNHH also ranked among the nation’s best in 12 of 16 medical specialties evaluated – including gynecology.

**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:

- 22 Chairs of Obstetrics and Gynecology
- 4 Deans of Medical Schools
- 5 Key Positions at the National Institutes of Health

**WHERE IN THE WORLD…**

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

*Francis Abibanna
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 Mohn, MD
John S. Mutterperl, MD
Ibrahim Sozen, MD*

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

**DID YOU KNOW?**

*Charles Lockwood, MD*, in his new role as Chair of the Yale Medical Group’s Board of Governors, was interviewed for the *Yale Practice* newsletter. Here is a link to the article: [http://www.yalemedicalgroup.org/physician/pdfs/julyaug09.pdf](http://www.yalemedicalgroup.org/physician/pdfs/julyaug09.pdf).
Catalin Buhimschi, MD and Anna Sfakianaki, MD, passed the Maternal-Fetal Medicine Boards. Chris Pettker, MD, passed his Ob/Gyn Boards. Congratulations!

Josh Copel, MD, is the Society for Maternal-Fetal Medicine (SMFM) President-Elect.

Pasquale Patrizio, MD, has been elected as a Fellow of the International Academy of Human Reproduction.

Eric Hodgson, MD, has been selected as one of eight physicians to be accepted into the Robert Wood Johnson (RWJ) Clinical Scholars Program for 2010-2012. He is currently a Fellow in the Maternal-Fetal Medicine program with his primary research area in obesity. He is specifically interested in examining how postpartum care of diabetic women can affect health and pregnancy outcomes.

Michael Paidas, MD, was a senior author on a paper published in June 2009 in both Hypertension and Obstetrics & Gynecology entitled “Pregnancy Complications Are a Stress Test for Future Maternal Health and Pregnancies.” The findings showed that among women with preeclampsia, the risks of subsequent hypertension were compounded with each affected pregnancy.

Joshua Johnson, PhD, was one of five Yale School of Medicine scholars to receive a Pilot Program grant from Women’s Health Research at Yale.

Yale was one of two institutions awarded the prestigious National Hemophilia Foundation Clinical Fellowship Program. The two-year Fellowship, which began in July 2009, is under the direction of Drs. Diana Beardsley, Peter Marks and Michael Paidas. Yale’s recipient of the Fellowship is Salley Pels, MD. She will spend two years developing advanced skills in clinical hemostasis and learning rigorous methodologies of clinical trial design, completion and monitoring.

Emre Seli, MD, received the Ira and Ester Rosenwaks New Investigator Award for his outstanding contributions to clinical or basic research in reproductive sciences within ten years after receiving a doctoral degree or completing residency training.

Gabor Huszar, MD, just celebrated 35 years at Yale within our Department. Congratulations!

CDR Mike Cackovic (MFM Fellowship Grad) delivered the first baby ever born aboard the USS Bataan, which is deployed in Operation Unified Response in Haiti. The mother successfully delivered an 8.3-pound boy!

Se-Te Joseph Huang, PhD, has been selected to receive a 2010 Albert McKern Scholar Award for Perinatal Research.

Elisabeth Erekson, MD, was first author on a paper entitled “The Association Between Stage II or Greater Posterior Prolapsed and Bothersome Obstructive Bowel Symptoms,” which was published in the January 2010 inaugural issue of Female Pelvic Medicine and Reconstructive Pelvic Surgery.

Thomas Rutherford, MD, PhD, has been appointed as a consultant to the Food and Drug Administration (FDA) Gastrointestinal Drugs Advisory Committee through February 5, 2015.
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 Torrealday, MD
Urogynecology & Reconstructive Pelvic Surgery: Madeline Dick, MD
Urogynecology & Reconstructive Pelvic Surgery: Sallis Yip, MD

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.

Online: Yale Netcasts

VISIT FRIENDS ON FACEBOOK

There are two new groups recently formed on Facebook where you can connect with Yale Ob/Gyn alums and fellow YOGS members:

Yale Obstetrics and Gynecology Society (YOGS) is comprised of current and former students, residents and clinical fellows who completed their training at Yale, as well as past and current faculty members. Here you’ll find YOGS updates, pictures and announcements of events. On Facebook, search Yale Obstetrics and Gynecology Society or visit:


Yale Ob/Gyn, developed by Dr. Samuel Pauli, a 2008 graduating resident, is open to all doctors, nurses and support staff currently or formerly associated with Yale Obstetrics and Gynecology. It is meant to allow old friends to reconnect and share announcements, both personal and professional. On Facebook, search Yale Obstetrics and Gynecology or go to:


Additionally, you can visit the following Yale-affiliated blogs and Facebook pages:

**BLOGS**

**Yale Fertility Center Blog:** [http://yalefertilitycenter.blogspot.com/](http://yalefertilitycenter.blogspot.com/)

**Yale Reproductive Endocrinology Blog:** [http://yalereproductiveendocrinology.blogspot.com/](http://yalereproductiveendocrinology.blogspot.com/)

**FACEBOOK PAGES**

**Yale RE:** [http://www.facebook.com/pages/Yale-Reproductive-Endocrinology/68087952760](http://www.facebook.com/pages/Yale-Reproductive-Endocrinology/68087952760)


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
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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.
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