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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editor’s Note</td>
<td>2</td>
</tr>
<tr>
<td>Historical Note</td>
<td>3</td>
</tr>
<tr>
<td>Residents’ Research Day Visiting Professor Grand Rounds</td>
<td>4</td>
</tr>
<tr>
<td>Other Selected Grand Rounds Presentations</td>
<td>6</td>
</tr>
<tr>
<td>Residents’ Research Day - Abstracts of Resident Presentations</td>
<td>23</td>
</tr>
<tr>
<td>Abstracts from Recent Scientific Meetings</td>
<td>29</td>
</tr>
<tr>
<td>The Year in Review</td>
<td>38</td>
</tr>
<tr>
<td>Photo Highlights</td>
<td>46</td>
</tr>
<tr>
<td>News Items</td>
<td>50</td>
</tr>
<tr>
<td>Forms</td>
<td>59</td>
</tr>
</tbody>
</table>
Another momentous year here in New Haven! As most of you know, despite the many charms of New Haven, Dr. Lockwood has left us to assume the Dean’s post at The Ohio State University College of Medicine (no, he didn’t go to coach the football team). Dr. Peter Schwartz kindly assumed the role of acting chairman, so the Department has functioned normally. The search committee is quite active, and we have been told to expect our new chair by the beginning of the new academic year. As Dr. Ed Funai also was stolen away by the attraction of Columbus, Dr. Catalin Buhimschi has kindly stepped in as acting head of the Section of Maternal-Fetal Medicine.

Our Department continues to run extremely well, and we are pleased to bring you some of the highlights of the past year in this journal. As part of the celebration of the Yale Medical School’s 200th anniversary, Charly arranged a great series of Grand Rounds speakers; here we bring you some of the highlights. Dr. Gautam Chaudhuri was our Residents’ Research Day speaker in June; as one of the outstanding basic scientists in gynecologic endocrinology, he gave a very thought-provoking talk on free radicals and breast cancer. Dr. Nathan Kase presented another superb talk on PCOS, explaining, as he always does, how basic science translates to clinical medicine. Dr. John Queenan, the pioneer in Rh management, gave us a definitive update on that field. We also thought we would share some news of our faculty members’ global outreach efforts: Drs. Magriples, Erekson and Rutherford described some of their activities in Africa and Jamaica.

Of course, we will update you on the research and clinical progress of our sections and the progress of our trainees, who continue to go out into the world and promote our field.

We hope that many of you will be joining us here in New Haven on May 12, when we celebrate the career of Yale’s first female resident, Dr. Mary Lake Polan. Mary Lake, of course, exemplifies Yale’s strong tradition of excellence in research and clinical medicine; she will be speaking not only of her career, which encompassed all her activities here at Yale as a trainee and young faculty member, but also about the expansion of her interests into international health. We anticipate another day of terrific presentations from Drs. Jamie Grifo, Florence Haseltine, Roberto Romero and Stephanie Spangler.

I hope to see you all soon, and enjoy your visit back to Yale while reading these pages!

Mary Jane Minkin, MD, FACOG
HISTORICAL NOTE

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Reflections of a “Community Doc”

I have been associated with the Department of Obstetrics and Gynecology at Yale in one capacity or another since 1967. There have been many changes, but one constant remains: The private physicians have always been integral to the Department and large contributors to its success.

In 1973, after returning from a stint in the Air Force, I found that morning report was packed with private and university faculty six days a week, all heatedly debating patient care. The on-call room was a coed barracks that slept four. The fetal monitor filled an entire room. There were no fellows, and some of the private community voluntarily rotated on call as high-risk attendings.

Over the ensuing years, the private doctors remained important to the Department’s mission: interviewing resident candidates; taking morning report; giving lectures to medical students, residents and others; and sleeping in-house to cover residents when attending presence was mandated 24/7. The Department of Obstetrics and Gynecology became the role model for successful integration of community and university faculty for the entire medical center.

With all the changes in our field, I have watched with pride the continued contributions of private Obstetrician/Gynecologists to the teaching and administration of the Department. We remain central to the collegial atmosphere of learning and growth that our students, residents, fellows and faculty enjoy.
Free Radicals and Their Interactions: Implications in Breast Cancer

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. They also fall under the definition of free radicals. A radical is an atom or a group of atoms that has one or more unpaired electrons. Radicals can have a positive, negative or neutral charge. They are intermediaries in a variety of normal biochemical reactions. When generated in excess or not appropriately controlled, radicals can wreak havoc on a broad range of macromolecules. Radicals have extremely high chemical reactivity, which can explain their normal biological activities and also how they inflict damage to cells.

Radicals that are very important in biological systems are derived from oxygen and are collectively known as reactive oxygen species (ROS). The ROS that have been identified as playing an important role in the biological system are the superoxide anion (O$_2^-$), peroxide (H$_2$O$_2$), and the hydroxyl radical OH$^-$. These oxygen-derived radicals are generated constantly as part of normal aerobic life. They are formed in the mitochondria as oxygen is reduced along the electron transport chain.

The ROS can be beneficial as well as harmful. The beneficial effects include an impact on intercellular and intracellular cell signaling. Amongst those that are toxic is the effect of oxygen radicals on cellular membranes (plasma, mitochondrial and endomembrane systems), which is initiated by a process known as lipid peroxidation, a common target being unsaturated fatty acids present as membrane phospholipids.

Under normal circumstances, cells are able to defend themselves against ROS damage with enzymes such as superoxide dismutase, catalase, glutathione peroxidases and peroxiredoxins. Small molecule antioxidants such as ascorbic acid (vitamin C), tocopherol (vitamin E), uric acid and glutathione also play a role.

More recently, it was demonstrated that redox dysregulation originating from metabolic alterations and dependence on mitogenic and survival signaling through ROS represents a specific vulnerability of malignant cells that can be selectively targeted by pro- and antioxidant redox chemotherapeutics. Mitochondria in cancer cells are known to produce the superoxide radical (O$_2^-$), which can undergo spontaneous dismutation or by manganese superoxide dismutase (MnSOD) to hydrogen peroxide (H$_2$O$_2$). Catalase is present in the peroxisomes and also in the mitochondrial matrix. Catalase is the main enzyme that converts H$_2$O$_2$ to H$_2$O and O$_2$. Glutathione peroxidase plays a minor role as well. It is only in the presence of free metals that H$_2$O$_2$ can lead to the formation of OH$^-$ radicals, which can be damaging to biological membranes and probably responsible for the autoxidation of membrane lipids.

Superoxide (O$_2^-$) is produced by many types of cancer cells in much higher amounts compared to non-malignant cells. The two major sources of O$_2^-$ produced by malignant cells are from the NADPH oxidase and the mitochondria. The O$_2^-$ can undergo spontaneous dismutation or by manganese superoxide dismutase (MnSOD) in
the mitochondria to H$_2$O$_2$. There is increased expression of MnSOD in various cancer tissues, including that of ovarian cancer, squamous cell cancer of the esophagus, adenocarcinomas of the stomach and carcinoma of the breast.

It is therefore not surprising that there is an increased amount of H$_2$O$_2$ produced in cancer tissues. Most studies that have tried to elucidate the role of H$_2$O$_2$ in cancer have either added it exogenously or enhanced its production indirectly by treatment with external agents. The effects have been either proliferative and anti-apoptotic or apoptotic, depending on the effective concentration. Sub-micromolar concentrations (0.5µM) of H$_2$O$_2$ led to proliferation, whereas higher concentrations (>100µM) led to cytostasis. We have observed that H$_2$O$_2$ is produced in significantly higher amounts in human breast cancer cells when compared with normal breast epithelial cells. We also observed that the bioactivity of catalase as well as glutathione peroxidase is decreased in breast cancer epithelial cells when compared with normal breast epithelial cells. ShRNA for catalase further decreased catalase bioactivity in breast cancer cells and increased intracellular H$_2$O$_2$ levels, and that led to an increase in the proliferation of these cancer cells. Transfection of the breast cancer cells with either catalase or glutathione peroxidase led to a decrease in intracellular H$_2$O$_2$ levels, thereby leading to apoptosis. We have observed that H$_2$O$_2$ inhibits protein phosphatase 2A (PP2A), thereby ensuring that ERK1/2 and Akt remain in a phosphorylated state and leading to cell proliferation. Further understanding the mechanism of increased ROS in cancer and methods to reduce their endogenous levels may lead to slowing the growth of cancer.
It is an honor to participate in the Yale School of Medicine Bicentennial Celebration, as Yale has played such a major role in the development of perinatal medicine. In the preface of Management of High-Risk Pregnancy, there is a decade-by-decade chronicle of the advances in perinatal medicine (1), listing the individuals associated with these discoveries. Remarkably, nearly 20% of those worldwide advances were pioneered here at Yale.

There were many innovations over a short span, beginning in 1958 with Dr. Hon’s development of electronic fetal heart rate evaluation. In 1971 Dr. Gluck developed the L/S ratio to determine fetal pulmonary maturity. In 1972 Dr. Quilligan introduced fetal heart rate monitoring and also initiated the American Board of Obstetrics and Gynecology certification process for Maternal Fetal Medicine. In that same year Drs. Hobbins and Rodeck (London) pioneered clinical fetoscopy. In 1991 Dr. Lockwood reported on fetal fibronectin and preterm delivery, and in 2000 Dr. Mari demonstrated the value of middle cerebral artery Doppler for monitoring Rh disease. These achievements are a large part of the rich legacy of Yale obstetrics.

Rh-alloimmunization was once responsible for approximately 6,000 perinatal deaths annually in the United States, half fetal and half neonatal. Rh-negative mothers generally became immunized by transplacental hemorrhage of Rh-positive fetal blood during the last two trimesters and at the time of delivery. Little was known about the disease process until Drs. Landsteriner and Weiner discovered the Rh-antigen in 1940 (2). This discovery opened the floodgates for investigations into cause, diagnosis, treatment and, finally, prevention. Many of these major discoveries were made during a short period from the 1950s through the late 1970s. While the advances are presented in the categories of diagnosis, therapy and prophylaxis, many investigators worked on all three areas simultaneously. It is my aim to present some of the critical breakthroughs as I observed them in this remarkable worldwide effort.

**DIAGNOSIS**

In the 1950s clinicians were limited to history, examination and Rh antibody titers. Management required great clinical skills, but assessing fetal condition accurately was actually impossible. In 1954 Dr. Allen and colleagues reported that 96% (167/174) of mothers with anti-D titers of 1:32 or lower with no history of hydrops or stillbirth had live fetuses at 37 weeks’ gestation (3). With higher titers the risk of fetal death was much greater. Thus Dr. Allen and colleagues demonstrated that low antibody titers and a favorable history were reliable predictors of good outcomes (Figure 1).

Antibody concentrations are increasingly being reported as international units per milliliter. In 1992 Drs. Nicolaides and Rodeck showed that with low antibody anti-D concentrations equal to or <15 IU/ml, fetuses were at most mildly anemic (4).
Figure 1

<table>
<thead>
<tr>
<th>Indirect Coombs: Titers</th>
<th>1:32 or lower</th>
<th>1:64 or higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUD &lt; 37 weeks</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>Alive at 37 weeks</td>
<td>187</td>
<td>154</td>
</tr>
</tbody>
</table>

Allen, Diamond, Jones. NEJM, 251: 453, 1954

AMNIOTIC FLUIDΔ450 MU ANALYSIS

In England in 1965, Dr. Bevis reported the correlation of elevated amniotic fluid (AF) bilirubin with increasing severity of disease (5). Dr. Liley provided the world with a clinical tool when he published his graph in 1961 (6). After amniocentesis, the AF was scanned with a spectrophotometer that measured the amount of bilirubin expressed as deviation in optical density at 450 (ΔOD 450). Dr. Liley created a graph with three downward-sloping zones from 27 to 40 weeks’ gestation based on fetal condition and AF bilirubin levels. For the first time, clinicians had an accurate predictor of fetal condition.

Generally, the low zone indicated that the fetus was safe in utero, was gaining valuable maturity, and might even be Rh-negative. The upper zone indicated that the fetus was at risk of severe disease and could die in utero. The middle zone indicated that the fetus could remain in utero, and a follow-up AF scan was often done. This was an important breakthrough for clinicians, as mildly affected or Rh-negative fetuses could safely stay in utero. Severely affected fetuses had to be delivered to avoid fetal hydrops and death. For the first time, many babies were saved, but in the 1960s and 1970s early delivery was a risky option because the neonatal survival rates remained low for very premature babies.

In the 1980s at Georgetown University Hospital, we treated many patients with severe Rh disease before 27 weeks’ gestation, which prompted us to develop a new graph starting at 14 weeks and extending to term (7). Known as the Queenan graph, it was crafted with 789 AF ΔOD450s, many of which were serial values from the same patient. The graph had four zones (Figures 2 and 3). All of the ΔOD450s of Rh-negative fetuses were plotted, and the area was divided into two zones, the lower half termed Rh-negative, the upper termed indeterminate. Then AF ΔOD450 values for hydropic and severely anemic fetuses were plotted, and this zone was termed intrauterine death risk. Finally, the last zone between the two lower and the intrauterine death risk zones was termed the Rh-positive (affected) zone. The Queenan graph became widely used because it was based on obtaining serial AF ΔOD450s to determine trends and was accurate in predicting fetal condition.

Figure 2

AF ΔOD₄₅₀ Zones

Queenan, AJOG 1993;168:1370

In 1998 Drs. Scott and Chan compared the Queenan chart versus the Liley chart (8). Of the 72 AF ΔOD450s, half were performed before 27 weeks and included all four of the severely affect-
ed samples and 11 of the 13 moderately affected samples. The sensitivity of the Queenan chart in severely affected pregnancies was 100% with specificity of 79.4%, positive predictive value of 22.2% and negative predictive value of 100%. For prediction of moderate/severely affected pregnancies, it had a sensitivity of 83.3% with a specificity of 94.4%, positive predictive value of 83.3% and a negative predictive value of 96.3%.

**MIDDLE CEREBRAL ARTERY PEAK SYSTOLIC PRESSURE**
For many years investigators tested Doppler studies’ ability to evaluate fetal anemia. It was Yale’s Dr. Mari who led the cooperative study of the middle cerebral artery peak systolic pressure (9). This technique is fast, noninvasive, and has a 74% positive predictive value and 10% false positive rate (9) when estimating fetal anemia in red cell alloimmunization.

Dr. Oepkes, et al compared AF ΔOD450 to MCA Dopplers using fetal hemoglobin levels (10). They found MCA Doppler as accurate as or better than AF ΔOD450. Since the Doppler studies are noninvasive, obviously they have replaced amniocentesis in most instances.

In 2005 Dr. Gautier and associates showed that fetal RhD genotyping was an accurate test, which could be used clinically to identify the Rh-negative fetus that would not need further testing (11). With this advance and the excellent work of Dr. Mari, it is now possible to reserve invasive procedures for fetal therapy.

**TREATMENT**
In the early 1960s, clinicians using AF ΔOD450s could tell when a fetus was severely affected. However, neonatologists, as skilled as they were, could not save very premature babies, particularly when they were sick Rh-affected babies. Some severely anemic and hydropic fetuses were delivered only to die in the nursery. In 1963, Dr. Liley once again came to the rescue with a daring procedure, the intrauterine transfusion (12). For the first decade there was no real-time ultrasound for needle guidance. That didn’t appear until 1973.

Dr. Liley’s dilemma was encountering patients with severe fetal disease too early to deliver safely. A physician who practiced in Africa told him that intra-abdominal transfusions were used safely for anemic children in remote villages. Dr. Liley performed a transabdominal intraperitoneal fetal transfusion by placing paper clips on the mother’s abdomen as a guide before obtaining a roentgenogram to show where to direct the needle. The transfused Rh-negative blood passes through the subdiaphragmatic lymphatics into the thoracic duct and enters the fetal venous system. Of four fetuses treated, one was saved, and the era of fetal therapy was born.

Many modifications were made to intrauterine transfusions, using sonography to guide needle placement and using the umbilical vein as the route for intravascular fetal transfusions. Survival rates for fetal transfusions using seven different approaches were reported by Drs. Schumacher and Moise (13). Considering all 411 fetuses, good outcomes were achieved in 84%. In nonhydropic fetuses, good outcomes were achieved in 94%, compared to 74% in hydropic. The procedure loss rate was 1%-3%.

In 2004 Dr. Van Kamps and associates reported results of 593 intrauterine transfusions in 210 pregnancies (14). The overall survival rate was 86% and 78% for hydropic fetuses. The procedure loss was 1.7%.

The LOTUS study provided a long-term follow-up after intrauterine transfusion, focusing on neurodevelopmental impairment (NDI) (15). NDI consisted of at least one of these: cerebral palsy, severe developmental delay or bilateral deafness and/or blindness. There were 389 survivors out of 426 transfused fetuses. Complete data was available for 87% (338). NDIs were detected in 9% (31/338): bilateral deafness in three, cerebral palsy in five and severe developmental delay in 23 of the babies.

AF ΔOD450s, middle cerebral artery peak systolic pressures and intrauterine transfusions were outstanding advances. While these breakthroughs were occurring in obstetrics, the field of neonatol-
ogy was making enormous progress. Neonatologists developed the neonatal intensive care unit concept and improved the care of prematurity, neonatal anemia and hyperbilirubinemia. Their ingenuity and dedication are responsible for many of the advances in the care of Rh-affected babies.

RH-IMMUNE PROPHYLAXIS
For centuries it was believed that the maternal and fetal circulations were separate. The possibility that fetal cells could enter the maternal circulation was not understood. In 1954 Dr. Chown reported three anemic newborns whose mothers had fetal hemoglobin detected in their circulations (16), proving the concept of transplacental hemorrhage. Dr. Levine soon demonstrated that the Rh-negative mothers became immunized by transplacental hemorrhage while carrying Rh-positive fetuses.

As a third-year resident at the New York Hospital/ Cornell Medical Center, I was intrigued by the process of Rh-alloimmunization. Since the initial detections of antibodies most often occurred postpartum, I wanted to investigate how fetal blood entered the maternal circulation at delivery. Performed long before the existence of institutional review boards, this research was rigorously supervised (17). After the baby and placenta were delivered, 20ml of the mother’s chromate-tagged blood was instilled in the uterine cavity with the mother in Trendelenburg position. Maternal venous blood was drawn at 5-, 10-, 30- and 60-minute intervals, demonstrating a transfer of red cells and plasma into the maternal circulation (Figure 4). Trendelenburg position and anesthesia appeared to enhance transfer, whereas methyl-ergonovine appeared to be more effective in decreasing transfer than oxytocin. With the advent of RhIG, this research seemed less important, but it could still be a piece of the puzzle in autoimmune disease or AF embolus.

The Kleihauer-Betke (KB) stain was a technique enabling investigators to identify and quantify fetal erythrocytes in the maternal circulation (18). Many investigators used this tool to study transplacental bleeding as the pathogenesis of Rh erythroblastosis fetalis. I spent many years in my laboratory at Cornell in New York City studying mechanisms of maternal immunization. Of course, we knew transfusing incompatible blood to Rh-negative women or, even more tragically, the injection of paternal blood into an Rh-negative daughter for potential protection against infectious disease could cause Rh immunization. The main genesis of maternal immunization, however, was transplacental hemorrhage. This became fertile ground for investigators for almost a decade.

Our group at Cornell used the K-B stain to track fetal erythrocytes and fluorescent antibody techniques to track Rh-positive fetal erythrocytes as they entered the maternal circulation. The work of numerous investigators showed an interesting phenomenon. Some mothers had fetal cells identified in their circulations in the first trimester, though infrequent and very low in volume. There was a slight increase in the second trimester, but in the third trimester the frequency of the transplacental passage of cells increased to as high as 70% of mothers. Most mothers had fetal cells in their circulations postpartum (Figure 5). It became obvious that delivery was the main immunizing event. Another cohort of mothers had no fetal cells detected antepartum, but postpartum had a transient presence of fetal red cells (Figure 6). This cohort had fetuses that were incompatible
with the mother in the ABO system. It seemed obvious that the maternal incompatibility in the ABO blood group was removing the fetal cells with maternal antibodies, a concept that was compatible with the work of Dr. Levine (19).

Simultaneously, at Columbia Presbyterian Medical Center, Vincent Freda, John Gorman and Bill Pollock from Ortho Pharmaceutical had teamed up to test the hypothesis that the Rh-positive fetal red cells could be cleared with administration of Rh-antibody postpartum. To test this hypothesis, Freda injected Rh-negative prison volunteers with 10ml of Rh-positive red cells. Three days later Freda returned to the prison to inject half of the volunteers (study) with anti-Rh antibody. The other half (controls) received nothing. The study was repeated at monthly intervals for five months. At six months, 0 of the 4 treated were immunized, compared to 4 out of 5 of the controls. A second phase of the study brought the results to 0 of 9 (treated) immunized compared to 7 of 11 (controls). The experiment showed that anti-Rh antibody protected the volunteers from developing active immunization (20).

To test this discovery in patients, the Columbia team enlisted Elmer Jennings of Long Beach Memorial Hospital and me at Cornell Medical Center. Our protocol was to administer 5-6000 micrograms of Rh-immune globulin to Rh-negative mothers delivering Rh-positive babies who were ABO compatible with their mothers.

David Zimmerman, a medical writer, recognized the enormous import of these studies and began to chronicle our progress in order to write a book. The following is an excerpt from Zimmerman’s book, *Rh: The Intimate History of a Disease and Its Conquest* (21).

On Sept. 9, 1965 Dr. Singer of Ortho Pharmaceutical called a secret meeting at the Waldorf-Astoria to discuss the six-month results of the trials, which were reported and posted on a blackboard. Following the meeting, Ortho participants would not comment. But the clinical investigators emerged elated and could see no reason to keep secrets: John Gorman, Vince Freda, John Queenan and Alvin Zipursky were seated in a bar discussing the six-month results: 0 immunized/92 treated versus 21 immunized/94 controls.

Dr. Zimmerman asked, “Do these figures have statistical significance?”

“As the figures were posted on the blackboard, we could see it was proven,” added John Gorman. “Then Dr. Zipursky dropped a bombshell,” he explained. “He had been injecting anti-Rh antibody, not at delivery as everyone else was doing, but as small divided doses during pregnancy, as everyone feared to do. Dr. Zipursky believed that immunization occurred before delivery. So he had been injecting small doses of 7S antibodies, small enough to prevent immunization but not large enough to harm the fetus.” On his notepad John Gorman had jotted: “Dr. Zipursky broke through a barrier. Can give 7S in pregnancy.”
The postpartum prophylaxis concept proved successful in our small clinical trial. It was now time to add more centers to test a much lower 300 microgram dose on a large scale to gain FDA approval.

Simultaneously and independently, the Cyril Clarke team in Liverpool was working on the same problem, and the race was on to see if a clinically proven program of postpartum administration of anti-Rh antibody (passive immunization) could prevent active immunization in the Rh-negative mother. Their progress was well known to us as we each presented our findings at scientific meetings and in research reports in the literature. Both teams arrived at successful large-scale trials at the same time, proving that postpartum Rh-antibody could prevent Rh immunization.

The acceptance by clinicians was slower than expected. The success of postpartum Rh-prophylaxis was reported frequently at scientific meetings and in journal articles. It proved successful in preventing 90% of immunizations in mothers who heretofore became immunized during pregnancy. We observed an impressive drop in the number of new immunizations. But curiously, even though this was a lifesaving measure, full utilization took almost 10 years to achieve (Figure 7) (22).

At a meeting in Boston in 1978, Dr. Bowman presented Canadian data with antepartum Rh-immune globulin at 28 and 34 weeks, aimed at preventing the 10% not protected by postpartum Rh-immune globulin (23). Most skepticism centered on the expense of giving prophylaxis unnecessarily to mothers carrying Rh-negative fetuses, estimated to be as high as 40%. But Dr. Bowman prevailed as his data showed that the targeted 10% of patients not protected by postpartum Rh-prophylaxis could be effectively protected. A two-dose regimen evolved, 300 micrograms at 28 weeks and again postpartum. Surprisingly, the utilization was almost immediate (Figure 7). At the time of postpartum RhIG introduction, perhaps the education and promulgation of a new procedure was not as efficient, but I suspect the rapid compliance with antepartum RhIG was a result of the current professional liability crisis, which fostered a climate of immediate adherence to standards of care.

The results of Rh-immune prophylaxis are evident today. The incidence of Rh disease is very low, and the loss of a baby is even rarer. But has the problem gone away? Unlike active immunization as used in rubella, poliomyelitis and tetanus, the prophylaxis for Rh-disease is passive. The clinical vigilance and the need for protection have not changed. All significant exposures to Rh-antigen must be covered with RhIG. Figure 8 is a presentation of the risk of Rh immunization in various clinical situations with degree of risk.

**Figure 8**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Abortion</td>
<td>3.5%</td>
</tr>
<tr>
<td>Induced Abortion</td>
<td>5.5%</td>
</tr>
<tr>
<td>Ectopic Pregnancy</td>
<td>less than 1%</td>
</tr>
<tr>
<td>CVS</td>
<td>small but unknown</td>
</tr>
<tr>
<td>Multifetal Reduction</td>
<td>small to moderate</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>3-5%</td>
</tr>
<tr>
<td>Third Trimester Bleed</td>
<td>variable</td>
</tr>
<tr>
<td>Third Trimester</td>
<td>1-2%</td>
</tr>
<tr>
<td>Mismatched Transfusion</td>
<td>50-80%</td>
</tr>
<tr>
<td>Needle Sharing</td>
<td>high but unknown</td>
</tr>
</tbody>
</table>

**FUTURE**

RhIG is easily attainable in the United States, but this is not true for all countries, and shortages have occurred. The current system of production relies on pooled human plasma from actively immunized men. Development of a monoclonal
antibody would have the advantages of purity, lower cost and greater availability. But even with a monoclonal antibody, we still would be relying on the less than perfect system of passive immunization. In my judgment, we have a workable stopgap measure that miraculously has more than decimated the incidence of Rh-alloimmunization, but I am convinced that someday there will be a better answer than passive immunization. This remarkable three-decade period of discovery, diagnosis, treatment and prophylaxis of Rh-disease was the result of multinational cooperation in conquering the disease. Today Rh-disease rarely causes fetal or newborn deaths.
REFERENCES


The Polycystic Ovary Syndrome: In utero Origins of the Syndrome, Its Metabolic Burdens in Adulthood and in Pregnancy, and Its Intergenerational Transmission

INTRODUCTION

The polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting from 5% to 8% of reproductive-aged women. For decades it was known primarily as a prevalent cause of anovulatory oligoamenorrhea and infertility, complicated by dysfunctional uterine bleeding, acne and hirsutism. However, PCOS is now understood as a factor in promoting progressive lifetime health burdens for some affected women. These include the consequences of an assembly, over time, of hyperandrogenemia, central visceral fat accumulation and insulin resistance (Ins Res), leading to a cluster of metabolic risk factors collectively known as the metabolic syndrome (medS) (see Box 1). As a result, given the risk of cardiac/metabolic/endocrine dysfunction and disease evolving into adulthood, PCOS is now a challenge for all clinicians and biomedical scientists.

Although no single defining genetic flaw has been identified, there is an apparent genomic/epigenetic basis underlying the variable timing, initiation and intensity of PCOS. In most cases, PCOS gradually emerges as a distinct clinical entity in pre- and peri-pubertal and adolescent girls and evolves into its full form in late adolescence or early adulthood (see Box 2). An epigenetic reaction to an environmental challenge at any stage in the lifecycle, including in utero, leads to altered homeostatic set points that persist and propagate, even across generations.

The morphology of the polycystic ovary depicts a variable rate of activation and recruitment but otherwise normal follicle development and progression, which is arrested at the early antral stage. Normal numbers of primordial “reserve” follicles, normal numbers of primary and secondary follicles, and a rate of atresia emphasize the inherent “normalcy” of these follicles other than the pace of their development and their failure to proceed to dominant follicle maturation. Indeed,
the PCO morphology can be encountered in normal ovulatory women, in multiparous women at tubal sterilization procedures, and in women on long-term steroidal contraception medication.

Regardless of what therapy is applied – weight loss, exercise, insulin sensitizers, gonadotropin enhancement with HMG or recombinant human FSH, or modulation with estrogen agonists/antagonists – the PCO is capable of surprising resiliency with swift recovery of apparently normal albeit therapeutically induced cyclic oscillations and ovulation.

In summary, the PCO ovary, in most instances, is inherently physiologically normal. It is inhibited by imposed intra- and extra-gonadal factors. When this inhibition is eliminated or reversed, normal function is restored. But with restoration and induction of ovulation and fertility, PCOS women still face additional problems.

**PCOS AND PREGNANCY COMPLICATIONS**

1. When pregnant, PCOS mothers are at increased risk of:
   - Pregnancy-associated hypertension preeclampsia
   - Gestational diabetes
   - Pregnancy loss, premature delivery
   - Cesarean section, birth canal trauma

2. Pregnancy in PCOS mothers adversely affects the fetus:
   - Large for gestational age (LGA), macrosomia
   - Small for gestational age (SGA)
   - Intrauterine growth retardation (IUGR)

3. Affects the neonate:
   - Birth trauma, shoulder dystocia
   - Neonatal hypoglycemia, hyperbilirubinemia
   - Elevated C-peptide levels in cord blood
   - Admission to NICU

4. Progeny (female) of PCOS mothers face lifelong (infancy through late adult life) risk of all or individual elements of the metabolic syndrome as well as recurrence of PCOS, CV disease, DM 2 and endometrial cancer.

**ACOG Practice Bulletin # 108, October 2009 (citations 30 – 45)**

**RATIONALE FOR PROPOSED STUDY**

When pregnant, PCOS women face triple the risk of developing gestational diabetes and 3.5 times the risk of developing hypertension/preeclampsia.

**HYPERTENSION AND PREECLAMPSIA**

Although the prospects for early predictive first trimester identification of the pathophysiologic mechanisms underlying the placental deficiencies (size, depth of invasion, degree of remodeling of the spiral arteries) that were the precursors to the emergence of preeclampsia later in pregnancy may finally be a reality, opportunities for safe intervention/therapeutic modification, if not reversal, are not available for first trimester interventions (hazards of inducing teratogenicity in the fetus, maternal hypotension). What is available are reactive responses to emerging classical signs of excess weight gain, edema, proteinuria or incipient rises in blood pressure followed by standard management, hopefully until safe induction of labor. Delivery is the only “cure.” Emerging but not widely tested and confirmed as useful are maternal markers of incipient, evolving, worsening severity of impending preeclampsia. These are sFlt-1, PLGF and s-Endoglin, among others. None of the current elements of care, although ameliorative – even expert meticulous prenatal care in large academic centers affiliated with research universities – totally avoid serious maternal and neonatal morbidities.

**GESTATIONAL DIABETES**

In dealing with the risk of gestational diabetes occurring in PCOS mothers, the challenge is not identifying those with subclinical or occult, unrecognized overt DM2 in the non-pregnant state.
The parameters evaluating glucose regulation established by the ADA and the IADPSG, utilizing criteria for FG, OGTT, HgA1c and a variety of family and personal history items, perform well on serial sequential measurements. Rather, the difficulty in determining abnormal glycemic control during pregnancy, once thought to be well established, is no longer considered definitive. The thresholds for diagnostic definition of pathologic dysglycemia resulting from the compounding influences of feto-placenta induced insulin resistance, the degree of maternal insulin resistance and limited maternal beta cell reserve (which correlates with fetal neonatal and maternal morbidities) have been upset by the large HAPO study. In this report the risk of adverse outcomes continuously increased as a function of glycemia at 24-48 weeks, gestation, even within ranges previously thought to be well within the scope of normal. Indeed, for most complications, “no threshold for increased risk could be defined.” The problem therefore is not the effectiveness of diet, exercise and insulin (or metformin) management in the reduction of these burdens, but when and in whom these strategies should be employed.

Furthermore, in both conditions (preeclampsia and gestational diabetes), early adverse fetal epigenetic programming in reaction to under-/over-nutrition condemns the fetus to lifelong adverse and accelerating cardio/metabolic dysfunction and disease. In addition, these circumstances lead to intra- and transgenerational transfer and retention of these risks in future generations. These issues crystallize the most serious limitation of reactive strategies for exclusively antenatal control of these disorders. Therapeutic interventions restricted to the latter half of pregnancy deny the possibility of first trimester correction of the initiating abnormalities of placental function and the adverse permanent epigenetic programming the fetus undertakes to cope with these conditions.

**HYPOTHESES**

**BASIC PRINCIPLES:**

- A correlation of epigenetic biomarkers with acquired, compounding “environmental stresses” needs to be developed for early-stage diagnoses.

- The paradigm that genetics is the primary molecular mechanism involved in biology and medicine needs to be modified to include epigenetics as a crucial regulatory factor as well.

1. **The pre-pregnancy cardio/endocrine/metabolic status of the PCOS woman is correlated with development of pregnancy complications.**

The PCOS phenotype emerges progressively from early infancy through childhood and adolescence and into adulthood. In the more severe forms, the defining attributes (*i.e.*, obesity, hyperandrogenism and insulin resistance) may be seen as early as childhood (obesity, premature pubarche, sleep apnea). As this developmental evolution accelerates, by late adolescence and post-adolescence the majority of PCOS young women in the U.S. demonstrate some evidence of the metabolic syndrome; *i.e.*, hypertension, dyslipidemia, impaired glucose tolerance and increased visceral (abdominal) adiposity. The advent of pharmacologic induction of ovulation and pregnancy in these women does not mean that they are spared the cardio/metabolic burdens of the syndrome and increased prospect of complication arising in pregnancy. Pregnant PCOS mothers face increased risks of developing intragestational hypertension and preeclampsia and gestational diabetes mellitus resulting from the initial presence and incremental deterioration of cardio/endocrine/metabolic status that the pregnancy imposes.

**QUESTION TO TEST HYPOTHESES:**

Will pre-pregnancy identification of particular risk factors and specific corrective therapy reduce the intra-pregnancy burdens of the PCOS mother and her fetus?

2. **The intra- and intergenerational transmission of PCOS is caused by intrauterine fetal epigenetic reprogramming in reaction to PCOS maternal “constraints.”**
The pathophysiologic burdens arising in pregnancy are not limited to the PCOS mother; they impose serious constraints on the well-being of the entirely dependent, developing fetus. In order to modify the impact of these adverse maternal circumstances (hypertension, hyperglycemia, hyperlipidemia) and maximize fetal well-being, reactive fetal epigenetic protective reprogramming strategies are initiated. Accordingly, homeostatic set points are modified to shift fuel and nutrient distribution, utilization and storage and prioritize the degree of fetal organ development, growth and function. However well these strategies compensate and accommodate – ”match” – the constrained intrauterine environment, their effects are maintained and even propagate after birth. Accordingly, in the nutritionally deprived SGA or IUGR fetus, they may not match (”mismatch”) the extra-uterine environment encountered after birth. The reprogrammed homeostatic set points and their consequences are no longer protective. Rather, these increase the vulnerability of child, adolescent and adult to the burdens inherent in the behavioral and dietary characteristics of developed societies. Similarly, the LGA fetus, through over-nutrition (maternal hyperglycemia and hyperlipidemia), enters extra-uterine life already burdened by visceral adiposity and hepatic steatosis. In both types of PCOS progeny, incremental cumulative burdens experienced from childhood through adulthood, consisting of lipotoxicity, glucotoxicity and a systemic inflammatory state, inevitably increase the risk of eventual cardiovascular disease, diabetes mellitus and cancer in the adult progeny of PCOS women.

Obesity and Pregnancy Are Associated with Insulin Resistance and Inflammatory Changes That Exacerbate in Combination, Increasing Lipid Transfer Earlier in Gestation

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AJP - Regulatory, Integrative and Comparative Physiology
Rwanda - Obstetric Fistula

Obstetric fistula is a devastating maternal morbidity commonly found in third-world countries where access to obstetric care is limited or nonexistent. This preventable condition results from prolonged obstructed labor, sometimes lasting three to four days. It commonly occurs in primiparous adolescents, owing to cultures in which girls marry young and fertility enhances social status. Obstetric fistula involves urologic, gastrointestinal and gynecologic injuries, resulting in urinary and sometimes fecal incontinence. Socially, women with this condition are ostracized and abandoned by their husbands and family, and often live isolated in shame and poverty. A 2010 estimate shows approximately two to three million women in Asia and sub-Saharan Africa suffering from fistula, and the World Health Organization estimates between 50,000 and 100,000 new cases each year.

The Republic of Rwanda is one of the many African countries in which women are affected by obstetric fistula. Roughly the size of Maryland, Rwanda is located in east-central Africa and is home to 11.4 million people, more than half of whom are under 18 years old. This is largely due to the infamous 1994 genocide in which an estimated one million people were killed. Since the genocide, Rwanda has begun a rebirth under the leadership of President Paul Kagame. One of the many accomplishments thus far has been the institution of national health insurance, which covers 92% of the population. However, the quality of healthcare is still very limited. This is in part due to the lack of qualified medical professionals, many of whom were killed or fled the country during the genocide. The recent ratio estimates one physician for every 18,000 residents.

Maternal health in Rwanda is gradually improving, in part due to the training of healthcare professionals and increased access to obstetric care. According to the United Nations Population Fund, approximately 63.5% of births were attended by a skilled health worker in 2010. Their fistula program also provided surgical repair to 245 women between January and September 2010. Visiting surgeons have further assisted fistula repair rates and native physician training. However, additional improvements are needed and recognized by the Rwanda Ministry of Health for both the prevention and management of obstetric fistula. These include enhancement of their fistula program, focus on emergency obstetric and neonatal care, improved access to contraception, and partnering with training institutions.

The International Organization of Women and Development (www.iowd.org) is an organization dedicated to the prevention of obstetric fistula, treatment of fistula and education of these women. A team of urogynecologists, colorectal surgeons, urologists, anesthesiologists and nurses has traveled to Rwanda three times per year (October, January and April) since April 2010, completing five missions to date. In April 2011, the IOWD performed 25 fistula repairs and 10 other major gynecologic surgeries. Rwanda provides a unique and exciting opportunity to train native physicians and nurses. We have begun an
outreach program of former fistula patients to the rural communities to teach women basic antenatal care, how to seek help and ways to prevent fistula. I will be returning to Rwanda in April 2012.
In October 2011, Dr. Thomas J. Rutherford returned to Jamaica as part of a medical mission in association with Sacred Heart University. A total of 37 healthcare professionals were involved, including 10 nursing students and four nurse practitioner students as well as YNHH community members Leroi Stephenson, MD, Anesthesiology; Connie Chu, CRNA; Porscha Benjamin, surgical technologist; and Dana Marie Roque, MD, Gynecologic Oncology fellow. The group brought with them multiple suitcases filled with medications and surgical supplies.

Over the course of one week, the general surgery and gynecologic teams performed a total of 44 procedures, including abdominal hysterectomy, Bartholin’s gland excision, abdominal and inguinal hernia repair, and cholecystectomy, at St. Joseph’s Hospital in Kingston. Some patients traveled over three hours by bus to obtain care. Medical teams staffed outreach clinics that provided internal medicine, pediatric and gynecologic services to surrounding rural communities and villages such as Braes River, Glenn Hope, St. Elizabeth’s Church, Tivoli Gardens and Santa Cruz. Collectively, as many as 100 patients were evaluated per day.

Sister Grace Yap, founder of the Franciscan ministries in Jamaica, coordinates this effort annually. She also helps to educate visiting volunteers about Jamaican culture, socioeconomics and barriers to healthcare access. At the conclusion of the week, all undistributed healthcare goods were donated to the community.
In the years following the 1994 genocide, the Republic of Rwanda has made great strides in development, with particularly notable achievement in the health sector. With near universal health insurance coverage and one of the fastest-falling infant mortality rates ever recorded, Rwanda is focused on developing a sustainable pipeline of skilled healthcare professionals to support continued development. Yale joined the Rwanda Health Education Consortium last year with specific focuses in the areas of internal medicine, pediatrics, obstetrics and gynecology, and health management. Yale will be collaborating with several other United States universities to strengthen medical student and resident education as well as healthcare delivery.

There are estimated to be 480 trained physicians in Rwanda (one doctor for every 18,000 people) and only 11 Obstetrician/Gynecologists. The Consortium plans to hire United States physicians for a minimum year-long commitment to work in Rwanda as well as rotating subspecialists to train medical students and residents in obstetrics and gynecology. This will also provide an opportunity for Yale residents to rotate on elective in Rwanda. The proposal has been funded for five years and will begin July 2012.
BACKGROUND

Chronic inflammatory environment and enhanced cell survival (i.e., balance between proliferation and apoptosis) play prominent roles in the establishment and progression of endometriosis. The p38 MAPK pathway transduces signals from the cell membrane to the nucleus in response to a wide range of cellular stimuli and environmental stresses. p38 MAPK regulates a variety of cellular functions including cytokine production, proliferation, and apoptosis. The aims of this study were to determine the expression and activity of p38 MAPK in normal and endometriotic human endometrium, and to evaluate its regulatory effect on cytokine production and cell survival in endometriosis.

METHODS

Comparison of p38 MAPK expression and phosphorylation throughout the menstrual cycle in normal and endometriotic human endometrium was performed with immunohistochemistry. IL-8 expression and apoptosis were evaluated in endometriotic implants with immunohistochemistry and TUNEL assay, respectively, and correlated with p38 MAPK activity in vivo. Western blot analysis was performed to investigate the effects of proinflammatory cytokines (TNF-α and IL-1β) on p38 MAPK activation in cultured endometriotic cells. The role of p38 MAPK in the regulation of proinflammatory cytokine-induced IL-8 and MCP-1 expression in cultured endometriotic cells was investigated with ELISA. TUNEL, BrdU and MTT assays were performed to evaluate the effect of the p38 MAPK pathway on cell survival in endometriotic cells in vitro. The data were analyzed with Student’s t-test, one-way ANOVA followed by post hoc Holm-Sidak test or Pearson correlation test. Statistical significance was defined as p<0.05.

RESULTS

p38 MAPK activity (phosphorylation) was significantly higher in eutopic and ectopic, epithelial and stromal cells of endometriosis patients compared to those cells in normal endometrium during late proliferative and early secretory phases (p<0.05). Moreover, phosphorylated p38 MAPK levels in epithelial cells of ectopic endometrium of endometriosis patients were significantly higher than those of the same patients’ eutopic endometrium (p<0.05). Phosphorylated p38 MAPK expression was significantly higher in both epithelial and stromal cells of the superficial ectopic endometrial implants compared to those of deeper implants of the same sample.

Increased MAPK activity in endometriotic cells was correlated with IL-8 expression (Pearson correlation coefficient r=0.83, p<0.01), but not with apoptosis in vivo. IL-1β and TNF-α induced p38 MAPK phosphorylation and, in turn, stimulated MCP-1 and IL-8 expression in cultured endometriotic stromal cells (p<0.05). This proinflammatory cytokine-induced MCP-1 and IL-8 production was blunted by a specific p38 MAPK inhibitor, SB203580, in endometriotic stromal cells in vitro. However, blockage of the p38 MAPK pathway did not change the survival of the cultured endometriotic cells.

CONCLUSION

Enhanced p38 MAPK activity may contribute to the inflammatory environment in endometriosis. Although the p38 MAPK pathway is not directly involved in the survival of ectopic endometriosis implants, the inflammatory environment created by p38 MAPK may result in establishment and progression of endometriosis.
Differential Sensitivity to Platinum-Based Chemotherapy in Primary Uterine Serous Papillary Carcinoma Cell Lines with High vs. Low HER-2/neu Expression \textit{In vitro}

Sarah N. Cross, MD; Emiliano Cocco, PhD; Stefania Bellone, PhD; Valsamo Anagnostou, MD; Stacey Brower, PhD; Christine Richter, MD; Eric Siegel, MS; Peter E. Schwartz, MD; Thomas J. Rutherford, MD; Alessandro Santin, MD
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OBJECTIVE

We sought to identify effective chemotherapy regimens against uterine serous papillary adenocarcinoma (USPC).

STUDY DESIGN

Six USPCs, half of which overexpress HER-2/neu at 3+ level, were evaluated for growth rate and \textit{in vitro} sensitivity to 14 single-agent chemotherapies and five combinations by ChemoFx (Precision Therapeutics Inc., Pittsburgh, PA).

RESULTS

Cell lines overexpressing HER-2/neu showed higher proliferation when compared to low HER-2/neu-expressing cell lines and a lower half maximum inhibitory concentration [IC(50)] when exposed to the majority of single-agent chemotherapies. High HER-2/neu expressors were more sensitive to platinum compounds, manifesting a 5.22-fold decrease in carboplatin-IC(50) \textbf{(P} = .005) and a 5.37-fold decrease in cisplatin-IC(50) \textbf{(P} = .02). When all cell lines were analyzed as a group, chemotherapy agents tested demonstrated lower IC(50) when used in combination than as individual agents.

CONCLUSION

USPCs overexpressing HER-2/neu display greater \textit{in vitro} sensitivity to platinum compounds when compared to low HER-2/neu expressors. Higher proliferative capability rather than increased drug resistance may be responsible for the adverse prognosis associated with HER-2/neu overexpression in USPC.
Maternal Infection in Pregnancy and Risk of Asthma in Offspring

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OBJECTIVE

This study sought to estimate the effect of maternal infection during pregnancy on asthma development in children, which has been debated in the literature.

METHOD

We followed 1,428 pregnant women and their children prospectively, using structured interviews and medical record review until the child’s sixth year of life. Infections during pregnancy were identified for hospital admissions, emergency department visits and problems identified as outpatients. Asthma in children was defined as physician diagnosis with current symptoms at age six. Adjusted odds ratios (ORa) were calculated from multivariable logistic regression models.

RESULTS

There were 635 women (44.5%) who experienced an infection during pregnancy: 21.1% had respiratory infections, 19.0% urinary tract infections, 13.9% gynecologic infections and 4.8% chorioamnionitis. Having any antepartum infection in pregnancy was associated with childhood asthma (ORa 1.49, 95% CI 1.07-2.07); however, among the specific infections, only antepartum urinary tract infection was significantly associated (ORa 1.48, 95% CI 1.03-2.12). Rectovaginal colonization with group B streptococcus was reported for 20.9% of women but was not found to be associated with childhood asthma (ORa 1.29, 95% CI 0.90-1.84).

CONCLUSION

This study found an increased risk of asthma in children of women diagnosed with urinary tract infections during pregnancy, while other maternal infections did not appear to be associated with asthma in offspring. Maternal and fetal immune and inflammatory responses to urinary pathogens, as well as alterations in microflora associated with infection and antibiotic exposure, may present a unique set of circumstances that predispose to an atopic state in offspring.
HOXA10 Regulates Expression of Cytokeratin 15 in Endometrial Epithelial Cytoskeletal Remodeling

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OBJECTIVE

The mammalian cytoskeleton is composed, in part, from intermediate filaments, of which keratin is an essential component. The keratin cytoskeleton forms a complex, highly dynamic intracellular network that can change in response to cell cycle changes and cellular movement and differentiation. Here we investigate the expression of CK15 in the human endometrium and its regulation by HOXA10 in the human endometrial cell lines.

METHODS

Endometrial biopsy specimens from throughout the menstrual cycle (N=32) were evaluated for CK15 protein expression by immunohistochemistry, using a mouse monoclonal antibody. The human endometrial stromal cell line (HESC) and human endometrial epithelial cell line (Ishikawa) were transfected at 60%-70% confluence with pcDNA/HOXA10; transfection with empty pcDNA vector served as a control. Transfections were performed in triplicate and repeated twice. Seventy-two hours after the transfection, total RNA was isolated. Quantitative RT-PCR was performed to determine expression levels of CK15. Results were compared using a non-paired t-test.

RESULTS

In the peri-implantation window (days 16 through 23), CK15 protein expression in the glandular epithelium of the human endometrium decreased to 50% of the proliferative phase expression level. CK15 mRNA expression decreased by 99% (p<0.05) after pCDNA/HOXA10 transfection of Ishikawa cells. CK15 was not regulated by HOXA10 in HESC cells, and no significant variation was observed in CK15 expression in stromal endometrial cells throughout the menstrual cycle.

CONCLUSION

CK15 gene expression is decreased in a HOXA10-dependent fashion in human endometrial epithelial cells. Expression decreases in the peri-implantation period concurrent with maximal HOXA10 expression. Dramatic changes in cellular architecture are necessary to achieve the secretory changes in the endometrial epithelium that bring about the implantation window. Alterations in CK15 likely facilitate these cytoskeletal changes, ultimately promoting endometrial receptivity.
Cisplatin (C) and Ifosfamide (I) Chemotherapy with Vaginal Cuff Brachytherapy (VCBT) for Treatment of Uterine Carcinosarcoma

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BACKGROUND

Uterine carcinosarcoma is an uncommon and aggressive type of uterine cancer with a poor prognosis. The purpose of this retrospective study is to report the efficacy and tolerability of C and I chemotherapy with VCBT in the treatment of uterine carcinosarcoma at Yale-New Haven Hospital (YNHH).

METHODS

Patients (pts) diagnosed with uterine carcinosarcoma in years 1996 – 2008 were identified through the Tumor Board Registry of YNHH. Demographic and clinical data including stage, histology, grade, dose, cycles, need for dose reduction, toxicities, co-morbidities, progression-free (PFS) and overall survival (OS) were obtained. Pts received C 40 mg/m² on day 1 and I 1.2 mg/m² daily on days 1 to 4 with Mesna every 4 weeks for 6 cycles. High dose rate intracavitary VCBT was delivered with a vaginal cylinder. A total of 14 Gy was delivered in 2 fractions of 7 Gy each prescribed to a depth of 0.5 cm. The two fractions were administered 2 weeks apart in cycles 1 and 2.

RESULTS

A total of 29 pts treated with C and I were identified, and 23 of 29 pts received VCBT. Median age of pts is 65 (range 40-82). There were sixteen pts (54.8%) with stage I/II, 8 (27.6%) with stage III, and 5 (17.2%) with stage IV disease. Eighteen (62%) pts completed C and I without a dose reduction, and 6 required a dose reduction, while 5 required early termination (3 of 5 pts completed <5 cycles). At median follow-up of 19 months (range 6-73), disease progression occurred in 9 pts (31%) and death occurred in 7 pts. With VCBT, no isolated vaginal failures were identified. Documented grade 3 toxicities included neutropenia (17%), anemia (14%), thrombocytopenia (3%), neurotoxicity (7%), fatigue (7%), nausea/vomiting (3%), hematuria (3%), cardiac toxicity (3%) and dyspnea (3%). Two pts (7%) had grade 4 neutropenia.

CONCLUSION

C and I chemotherapy with VCBT represents a well-tolerated regimen with promising activity for uterine carcinosarcoma. The addition of VCBT results in excellent local response.
Higher Sensitivity to Patupilone versus Paclitaxel Chemotherapy in Primary Uterine Serous Papillary Carcinoma Cell Lines with High versus Low HER-2/neu Expression In Vitro

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OBJECTIVE
To compare the in vitro sensitivity/resistance to patupilone versus paclitaxel in uterine serous papillary carcinoma (USPC) with high versus low HER-2/neu expression.

METHOD
Six primary USPC cell lines, half of which over-express HER-2/neu at a 3+ level, were evaluated for growth rate and tested for their in vitro sensitivity/resistance to patupilone versus paclitaxel by MTS assays. Quantitative RT-PCR was used to identify potential mechanisms underlying the differential sensitivity/resistance to patupilone versus paclitaxel in primary USPC cell lines.

RESULTS
Cell lines overexpressing HER-2/neu showed higher proliferation when compared to low HER-2/neu-expressing cell lines. Compared to low-expressing cell lines, high HER-2/neu expressors were significantly more sensitive to patupilone than to paclitaxel (p<0.0002). In contrast, there was no appreciable difference in sensitivity to patupilone versus paclitaxel in primary USPC cell lines with low HER-2/neu expression. Higher levels of β-tubulin III (TUBB3) and P-glycoprotein (ABCB1) were detected in USPC cell lines with high versus low HER-2/neu expression (p<0.05).

CONCLUSION
USPC overexpressing HER-2/neu display greater in vitro sensitivity to patupilone and higher levels of the patupilone molecular target TUBB3 when compared to low HER-2/neu expressors. Due to the adverse prognosis associated with HER-2/neu overexpression in USPC patients, patupilone may represent a promising novel drug to combine with platinum compounds in this subset of aggressive endometrial tumors.
ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the Society for Maternal-Fetal Medicine 32nd Annual Meeting, February 6-11, 2012, Dallas, Texas

ORAL PRESENTATIONS


Severe Preeclampsia (sPE) is Characterized by Dysregulation in the Proteolytic System of Amyloid Precursor Protein (APP) and Deposition of Amyloidogenic Aβ Fragments in the Placenta. I.A. Buhimschi, K. Trotta, C. Laky, G. Zhao, C.S. Buhimschi.

Fetuin-Mediated Aggregation of Amniotic Fluid Proteins into Calcifying Nanoparticles (CNP) and Preterm Premature Rupture of Membranes (PPROM). L.L. Shook, C.S. Buhimschi, A.T. Dulay, M.O. Bahtiyar, I.A. Buhimschi.

Metagenomic Based Comparative Analysis of the Amniotic Fluid (AF) and Cord Blood (CB) Microbiomes in Pregnancies Complicated by Intra-Amniotic Infection and Early-Onset Neonatal Sepsis (EONS). Y. Weng Han, X. Wang, S. Temoin, V. Bhandari, I.A. Buhimschi, C.S. Buhimschi.

Evidence for Presence of the Super-Interleukin-6 (superIL-6) Trans-Signaling Complex in Amniotic Fluid (AF) and Its Participation in the Intra-Amniotic Inflammatory Response to Infection. S.S. Abdel-Razeq, I.A. Buhimschi, K. Trotta, G. Zhao, M.O. Bahtiyar, C.M. Pettker, C.S. Buhimschi.


Excess Glucose Up-Regulates First Trimester Trophoblast Secretion of Pro-Inflammatory Cytokines and Chemokines and Reduces Anti-Inflammatory IL-10 Secretion. C.S. Han, S.F. Thung, N. Nickless, C.J. Lockwood, V.M. Abrahams.


Method of Delivery and Neonatal Outcomes in Preterm, Small for Gestational Age Infants. E.F. Werner, D.A. Savitz, T.M. Janevic, S.F. Thung, E.F. Funai, H.S. Lipkind.


POSTER PRESENTATIONS


Excess Glucose Levels Limit First Trimester Trophoblast Migration and Induce an Anti-Angio- genic Profile. C.S. Han, S.F. Thung, N. Nickless, C.J. Lockwood, V.M. Abrahams.


ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral Presentations at the Society of Gynecologic Oncologists 43rd Annual Meeting, March 24-27, 2011, Austin, Texas

POSTER PRESENTATIONS


ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the American Urogynecologic Society 32nd Annual Meeting, September 14-17, 2011, Providence, Rhode Island

ORAL PRESENTATIONS


POSTER PRESENTATIONS

ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS

Yale Oral and Poster Presentations at the American Society for Reproductive Medicine 67th Annual Meeting, October 15-19, 2011, Orlando, Florida

ORAL PRESENTATIONS


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

Loss of Embryonic Poly(A) Binding Protein (ePAB) in Mouse Results in Female Infertility Due to Impaired Oocyte Maturation and Ovulation. O. Guzeloglu-Kayisli, M.D. Lalioti, I. Sasson, D. Sakkas, F. Aydiner, E. Seli.


Embryonic Poly(A) Binding Protein (ePAB)-Deficient Male Mice Have Elevated MSY2 Expression in Testis. S. Ozturk, O. Guzeloglu-Kayisli, M.D. Lalioti, D. Sakkas, E. Seli.

Embryonic Poly(A) Binding Protein (ePAB) Plays a Key Role in Chromatin Remodeling and Transcriptional Silencing During Oocyte Maturation. O. Ilbay, O. Guzeloglu-Kayisli, M.D. Lalioti, E. Seli.


POSTER PRESENTATIONS

Variations of Short and Long Term Dehydroepiandrosterone (DHEA) Supplementation in Women with Diminished Ovarian Reserve (DOR) Based on FMR1 Ovarian Genotypes and Age. N. Gleicher.


Oocyte Yields per Anti-Müllerian Hormone (AMH) at Different Female Ages Change with Advancing Female Age: A New Tool to Assess Oocyte Quality? N. Gleicher, A. Weghofer.


Long Term Estradiol Treatment Improves Reproductive Parameters in Leptin Deficient Female Mice. J. Luk, T. Horvath, J. Johnson.


Functional Ovarian Reserve Comparisons Between Oocyte Donors and Infertility Patients to Demonstrate Different Ovarian Aging Patterns Between Races. N. Gleicher, A. Kim.


A Pilot Study Raising Concern about Utilization of Low Intensity IVF (LI-IVF) in Place of Standard IVF (S-IVF). N. Gleicher.


ABSTRACTS FROM RECENT SCIENTIFIC MEETINGS


ORAL PRESENTATIONS


* Selected as Abstract #1 of the Plenary Session
* The Giorgio Pardi Foundation Award for Top Four Abstracts


*Recipient of President’s Presenters Award


*Recipient of President’s Presenters Award

Treatment with Bone Marrow Derived Stem Cells (BMDSCs) Improves Fertility in a Murine Model of Asherman’s Syndrome. F. AlAwadhi, H.S. Taylor.


Cathepsin B Is Required for the Clearance of Dying Ovarian Follicles. J. Luk, R. Dawra, A. Saluja, J. Johnson.


Chlamydia Trachomatis Induces a Trophoblast IL-1β Response Through the Nod-Like Receptor, Nod1, and Not Through the Nalp3/ASC Inflammasome. V.M. Abrahams, C. Boeras, M.J. Mulla, P.B. Kavathas.

POSTER PRESENTATIONS


Pro-Inflammatory Signaling Pathway Mediation of IP-10 Expression in First Trimester Decidual Cells. S. Faramarzi, M. Rahman, N. Ocak, F. Schatz, C.J. Lockwood.


Premature Aging in Mice Exposed In Utero to Nonionizing Radiation Emitted from Cellular Telephones. T.S. Aldad, H.S. Taylor.

Metformin Prevents Insulin Induced Cellular Proliferation and Activation of Signaling Pathways in Endometrial Epithelial Cells. C. Flannery, D. Selen, H.S. Taylor.

In Utero Diethylstilbestrol (DES) Exposure Downregulates HOXA10, HOXA11 and Wnt7a Expression in Human Endometrium: A Case Study. K.E. Haines, H.S. Taylor.

Genome-Wide Methylation Profile Identifies Genes Involved in the Pathogenesis of Endometriosis. H. Naqvi, H.S. Taylor.


The Immune Balance of Tumor Necrosis Factor (TNF) Superfamily in Fetal-Maternal Interface in Response to Pro-Inflammatory Stimuli. M. Li, C.C. Yeh, J. Pecoriello, T. Cho, S. Pels, S.J. Huang.
The Regulation of Macrophage Polarization by Colony-Stimulating Factors from Pro-Inflammatory Cytokine-Stimulated First Trimester Decidual Cells. M. Li, C.C. Yeh, S. Pels, S.J. Huang.


The Role of Soluble N-ethylmaleimide-Sensitive Factor Attachment Protein Receptors (SNAREs) in Physiologic and Pathologic TF Transport in the Endometrium. G. Krikun.


THE YEAR IN REVIEW

WELCOME TO OUR NEW OB/GYN INTERNS

We are pleased to announce the interns for 2011-2012. All six are outstanding and highly accomplished physicians.

**SUDESHNA CHATTERJEE, MD – Jefferson Medical College of Thomas Jefferson University**

Sudeshna received her BA (Genetics, Cell and Developmental Biology) at Dartmouth College. She is a member of AOA and has membership in a number of honorary/professional societies. Sudeshna is involved in an ongoing research project entitled “Comparison of Wound Complications After Cesarean Section for Skin Incisions Made Above or Below the Pannus in Obese Women,” in which two abstracts will be submitted to the 2011 ACOG Annual Clinical Meeting. She volunteered in numerous organizations, including the Buduburam Refugee Settlement in Accra, Ghana. While at camp, she designed an HIV/AIDS curriculum for high school students and worked on the HIV/AIDS Community Outreach Team. Her hobbies and interests include playing the guitar, traveling and Bharatanatyam (Indian Classical Dance).

**STEPHEN COLLINS, MD, PhD – Emory University School of Medicine**

Stephen received his BS (Biology) at Pennsylvania State University and his PhD at Emory University School of Medicine. He is the recipient of numerous awards and a member of several honorary/professional societies. Stephen volunteered for a number of organizations during medical school, and was one of the founding members of the Penn State Nutrition Service Project, a service-learning group that sought to improve the health habits of children across central Pennsylvania through entertaining classroom visits focused on nutrition. He was actively involved in research projects, two of which resulted in two peer-reviewed articles and three poster presentations. His hobbies and interests include Major League Baseball, college football, church involvement, ethics and charity.

**CATHA FISCHER, MD – Mount Sinai School of Medicine of New York University**

Catha received her BA (Women’s Studies) at Washington University in St. Louis. At Mount Sinai, she achieved the top 10 percent of her class in the Clinical Skills Assessment Exercise, which indicates excellent integrative skills, clinical reasoning, professionalism and communication skills. Catha was involved in numerous volunteer and research projects during medical school. She was granted a 10-month scholarly leave by Mount Sinai to pursue academic research at Yale University School of Medicine under Dr. Hugh Taylor. During that time she focused on adenomyosis and endometriosis research, which ultimately led to multiple paper submissions, a poster presentation and oral presentations. Catha’s hobbies and interests include reading, cooking and watching baseball.
GREGORY GRESSEL, MD – Tufts University School of Medicine

Gregory received his BS (Philosophy, Theology, Biology) at Boston College. He was the recipient of numerous awards, including Student of the Year in the Department of Obstetrics and Gynecology. He is also a member of several honorary/professional societies. Gregory was involved in a number of volunteer and research projects during medical school. His research project on the psychological effects of dialysis and renal transplantation on patients with end-stage renal disease was accepted for publication in *Psychiatric Care of the Medical Patient*, 3rd Edition. Gregory is fluent in French and conversationally proficient in basic medical Spanish. His hobbies and interests include scuba diving, cooking, golf, kickboxing and French cuisine.

MATTHEW MACER, MD, PhD – The University of Southern California, Keck SOM

Matthew received his BS (Brain, Behavior and Cognitive Science) at the University of Michigan, Ann Arbor. He is a member of AOA and was the recipient of numerous awards. He was actively involved in numerous volunteer and research projects as well as with ACOG. Matthew spent a month in Peru, developing and living in a medical clinic, providing free medical care to a village of 340 Bora Indians. He also developed and taught seven classes of English to 24 Bora Indians. His hobbies and interests include competitive water-ski racing, learning new musical instruments and lacrosse.

MOHAK MHATRE, MD – Albert Einstein College of Medicine of Yeshiva University

Mohak received her BA (English) at Johns Hopkins University. She is a member of AOA. She was involved in numerous research projects. One of her research projects, “Role of seminal fluid in the HIV microbicide drug-delivery system,” was selected for participation in the Infectious Diseases Society of America Medical Scholars Program, and she received the Einstein Summer Research Fellowship. Mohak has two peer-reviewed journal articles/abstracts and one peer-reviewed book chapter. She is fluent in Spanish. Her hobbies and interests include hiking, biking and playing jazz piano.
Our 2011 Residency Program Graduates and Their Next Destinations

**HAKAN CAKMAK**  
Reproductive Endocrinology & Infertility Fellowship  
UCSF

**AMANDA KALLEN**  
Reproductive Endocrinology & Infertility Fellowship  
Yale University

**SARAH CROSS**  
MFM Ultrasound Fellowship  
Yale University

**CHARLENE HOOPER**  
Robert Wood Johnson Clinical Scholar  
Yale University

**KEN-YU LIN**  
Gynecologic Oncology Fellowship  
University of Texas Southwestern

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

**Aileen M. Gariepy, MD, MPH**, joins Yale as Assistant Professor in the sections of Family Planning and Comparative Effectiveness Research. Most recently, she comes from the University of Pittsburgh and Magee Women’s Hospital, where she completed her fellowship in Family Planning. During the fellowship, Dr. Gariepy also earned an MPH and completed the Physicians for Reproductive Choice and Health’s Leadership Training Academy. She is a *magna cum laude* graduate of Cornell University and earned her MD from MCP Hahnemann School of Medicine. Dr. Gariepy completed her residency in Obstetrics and Gynecology at Thomas Jefferson University Hospital where she served as Chief Resident. She then joined the faculty at Jefferson, earning a Berlex Foundation Junior Faculty Development Award and numerous teaching awards. During her fellowship, she served as co-investigator for multiple NIH-funded trials, including several for the Contraceptive Clinical Trial Network and the Microbicides Trial Network. Her research interests include decision analysis and comparative effectiveness in obstetrics and gynecology. She was recently awarded a Society of Family Planning research grant to study pregnancy rates after different sterilization methods. Dr. Gariepy looks forward to bringing her passion for patient-centered research, teaching and clinical care to Yale.

**Christina S. Han, MD**, joins Yale’s Section of Maternal-Fetal Medicine. Dr. Han completed the combined BS-MD program at the University of California (UC) at Riverside (2001) and UCLA (2004), where she was UC Regent Scholar and was awarded the William H. Dignam, MD Award for Excellence in Obstetrics and Gynecology. Dr. Han completed her residency training at Cedars-Sinai Medical Center (2008) in Los Angeles, and was active in the ACOG District IX Committee for Underserved Women, international medical missions and multiple hospital committees. She received the Gregory Dantzler, MD Chief Resident Teaching Award, Berlex Resident Teaching Award, Society of Laparoendoscopic Surgeons Outstanding Resident Award, and the Bruce and Sylvia Stern Resident Manuscript Award. Dr. Han then came to Yale as an MFM fellow from 2008-2011, where she has proved to be a highly productive fellow.

In 2010, she was awarded a position at Yale’s NIH-funded Women’s Reproductive Health Research (WRHR) career development program. Her research and clinical interests are focused around diabetes and metabolic disorders in pregnancy, particularly the pathophysiology of resulting aberrations at the maternal-fetal interface, the prevention of adverse pregnancy outcomes and *in utero* fetal programming. Additionally, with a strong interest in information technology, she is developing novel web- and smartphone-based technology platforms to enhance physician-patient, physician-physician and educator-trainee interactions. Dr. Han also serves on the Society of Maternal-Fetal Medicine Communications Committee and Education Outreach Subcommittee. Dr. Han speaks Mandarin Chinese, Taiwanese and medical Spanish. She resides in Wooster Square with her fiancé, Rodman Lau.
Lisbet Lundsberg, PhD, joins Yale as Associate Research Scientist/Scholar in the Comparative Effectiveness Research Section of Obstetrics, Gynecology and Reproductive Sciences. Dr. Lundsberg completed her PhD in Perinatal Epidemiology at the Yale School of Public Health in 1995. She subsequently joined the faculty of the Center for Perinatal, Pediatric and Environmental Epidemiology at Yale. Dr. Lundsberg has directed several large prospective cohort studies of pregnant women and their newborns, and was responsible for project management, supervising research staff, data collection, management and longitudinal follow-up. These studies include Nutrition in Pregnancy and most recently the National Children’s Study in Connecticut, a national study designed to examine the impact of the environment on over 100,000 pregnant women and their children. She has expertise in multivariable statistical analysis on large data sets of pregnant women and their newborns to investigate the relationship between selected risk factors, exposures and pregnancy outcomes. In her current position with the Section for Comparative Effectiveness Research and with her experience in data management, analysis and interpretation, she looks forward to collaborating with other faculty and trainees within the Department.

Winifred Mak, PhD, MBBS, joins Yale as Assistant Professor in the Reproductive Endocrine and Infertility section and as a Women’s Reproductive Health Research (WRHR) Scholar. She received her MD degree (MBBS) and a PhD in genetics from the Imperial College, University of London. She was an intern and resident in Ob/Gyn at St. Mary’s Hospital, the teaching hospital of the Imperial College. In 2003, Dr. Mak came to California where she spent a year as a visiting postdoctoral scholar at UCSF, followed by a residency in Ob/Gyn at Cedars-Sinai in Los Angeles. Afterwards she did an REI fellowship at the University of Pennsylvania. She already has a significant number of important peer-reviewed publications, including one as first author in Science. Currently, she is working as a WRHR Scholar in Dr. Haifan Lin’s laboratory in the Yale Stem Cell Center. Her research is concerned with the pumilio gene, a repressor of translation that appears to be involved in stem cell development, and its deletion has also been shown in mice to cause low fetal birth weights. Her clinical interests in the REI section are in IVF and infertility.
Nancy L. Stanwood, MD, MPH, joins Yale as an Associate Professor and Section Chief of Family Planning. This appointment is a homecoming for Dr. Stanwood. Born and raised in Connecticut, she graduated magna cum laude from Brown University and graduated from the University of Pennsylvania School of Medicine. She completed her Obstetrics and Gynecology residency at the University of Michigan and the Robert Wood Johnson Clinical Scholars Program Fellowship at the University of North Carolina, where she also earned her MPH. Before coming to Yale, Dr. Stanwood was at the University of Rochester School of Medicine & Dentistry. During her 10 years there, she successfully built and directed the Family Planning Service, including securing the Kenneth J. Ryan Residency Training Program Grant. She is an enthusiastic teacher, and among her awards is the prestigious National Faculty Award from the American College of Obstetricians and Gynecologists, Council on Resident Education in Obstetrics and Gynecology. Dr. Stanwood’s research interests include the underuse of intrauterine devices and prevention of teen pregnancies. She is a dedicated advocate for her patients and serves as the Secretary of the Executive Committee of Physicians for Reproductive Choice and Health. She is excited to bring her expertise and energy to the Yale and New Haven communities, as she finally comes home to her family in Connecticut.

Xiao Xu, PhD, MA, joins Yale as Assistant Professor in the Comparative Effectiveness Research Section of Obstetrics, Gynecology and Reproductive Sciences. Dr. Xu completed her PhD in Economics at Wayne State University and has been a research faculty member in the Department of Ob/Gyn at the University of Michigan since 2004. As a health economist, Dr. Xu’s research focuses on improving the efficiency and outcomes of healthcare delivery for women and older adults. Her recent projects have examined the cost-effectiveness of various medical and surgical interventions in obstetric and gynecologic care, the impact of insurance coverage on women’s healthcare utilization, gender and ethnic differences in older adults’ physical and mental health trajectories, and the influence of the state medical malpractice environment and liability reforms on physicians’ referral practice and the cost implications. Dr. Xu’s research has been funded by the Agency for Healthcare Research and Quality (AHRQ) and the Blue Cross Blue Shield of Michigan Foundation. She received Honorable Mention for the Aetna Susan B. Anthony Award from the American Public Health Association (Gerontological Health Section) for excellence in research on older women and public health (2005) and the Frank J. McDevitt Excellence in Research Award in Policy Research from the Blue Cross Blue Shield of Michigan Foundation (2008, 2011). She looks forward to developing new research collaborations in the Department and to working with students, residents and fellows at Yale.
New Fellows On Board July 1, 2011

Gynecologic Oncology: Dana Roque, MD
Maternal-Fetal Medicine: Karen Archabald, MD
Maternal-Fetal Medicine: Megan McCarthy, MD
Maternal-Fetal Medicine: John Hardy, MD
Reproductive Endocrinology & Infertility: Amanda Kallen, MD
Urogynecology & Reconstructive Pelvic Surgery: Alexandra McPencow, MD

Our 2011 Fellowship Graduates and Their Next Destinations

Heidi Chen, MD
Kaiser Permanente, Fontana, California

Karim ElSahwi, MD
Jersey Shore University Medical Center, Neptune, New Jersey

Christina Han, MD
Faculty of Yale University – Division of Maternal-Fetal Medicine, New Haven, Connecticut

Jennifer Kulp, MD
Genesis Reproductive Medicine, New York, New York

Erika Werner, MD
Johns Hopkins University, Baltimore, Maryland
PHOTO HIGHLIGHTS FROM THE APRIL 2011 ALUMNI REUNION IN NEW HAVEN, CONNECTICUT
PHOTO HIGHLIGHTS FROM THE APRIL 2011 ALUMNI REUNION IN NEW HAVEN, CONNECTICUT
PHOTO HIGHLIGHTS FROM THE 2011 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
PHOTO HIGHLIGHTS FROM THE 2011 C. LEE BUXTON RESIDENTS’ RESEARCH DAY
Healthcare for women changed dramatically in the early 1970s. Revolutionary changes to our profession, including fetal monitoring, ultrasound, radioimmunoassays and chemotherapy, were pioneered here at Yale. Equally profound changes affected the practitioners of our profession. This year at YOGS we are celebrating the most profound of these changes: the choice of the first woman resident at Yale. We are delighted to celebrate the career of Dr. Mary Lake Polan.

Mary Lake was no stranger to Yale when she started her residency here in 1975. She already had earned her PhD in Molecular Biophysics and Biochemistry at Yale in 1970, and had already done an NIH-sponsored postdoctoral fellowship with Dr. Joseph Gall when she started medical school here in 1972. Upon finishing her residency, she stayed on to complete her fellowship in Gynecologic Endocrinology and Infertility. What most of you don’t know is that Mary Lake also served for six months as the Gynecologic Oncology fellow. (Peter Schwartz wanted to remind you all of how much Mary Lake likes to cut!) She remained on faculty here until 1990, when the lovely weather in Palo Alto (and perhaps the school there) encouraged her to move to Stanford, where she became Chair of the Department of Obstetrics and Gynecology.

Mary Lake’s interests continued to expand. She earned an MPH degree in the Maternal and Child Health Program at the University of California, Berkeley. Those interests then led her to organize a team to travel to East Africa to treat fistulas and other obstetrical complications. She continues these activities to this day; her request to all of our speakers at our YOGS event was to comment on the international consequences of their work.

While at Stanford, Mary Lake was elected to the Institute of Medicine. She has advised the NIH on Opportunities for Research on Women’s Health. She has also served as an advisor to the Secretary of Health and Human Services. Of course, as a renowned bench researcher, she has hundreds of publications on many exciting topics, including ovarian function, steroidogenesis and endometriosis. Research interests currently include the interaction of the immune and endocrine systems.

Being an East Coast person at heart, Mary Lake finally left sunny California for New York, where she is now Visiting Professor at Columbia.

When asked to comment on her biggest obstacle, she replied to one interviewer, “Trying to raise a family and having a career are difficult to blend.” But she has accomplished both admirably, although her very talented daughter who attended our medical school could not be persuaded to become an Ob/Gyn!

Among Mary Lake’s other talents, which many of you do not know, is that she published an adventure novel in 1987, revolving around in vitro fertilization!
IN FOND MEMORY

Hilton Kort, MD

Dr. Hilton Kort died Friday, May 6, 2011 at the age of 64. A native of South Africa, Dr. Kort immigrated with his family to the United States in 1978 as a Ford Foundation Fellow at Yale University’s School of Medicine. Dr. Kort co-founded Reproductive Biology Associates, which pioneered the birth of the first baby in Georgia utilizing in vitro fertilization. Today, Dr. Kort’s practice is one of the preeminent IVF clinics in the world with close to 10,000 births. As a competitive endurance athlete, Dr. Kort was a two-time Ironman finisher and a three-time member of Team USA, competing in the Triathlon Age Group World Championships. A pillar in the community, Dr. Kort served as the Chairman of the Board of Trustees for Pace Academy. Hilton Kort is survived, revered and loved by his two sons, Anton and Jonathan, daughter-in-law Jackie and his wife of nearly 35 years, Philippa.

Elizabeth M. Sabga, MD

Dr. Elizabeth “Betsy” Sabga died on May 11, 2011 at the age of 50 at Bloomington Hospital. Dr. Sabga was born in Cleveland, Ohio, on January 22, 1961 and was educated at Harvard and Radcliffe colleges, the University of Cincinnati College of Medicine and the University of California at San Diego. She was board certified in obstetrics and gynecology and a fellow of the American Congress of Obstetricians and Gynecologists. She had practiced with Greater New Haven Ob/Gyn in Connecticut and with Aegis Women’s Healthcare as well as practicing gynecology with her partners, Brandt Ludlow and Betsy Birch, in Bloomington. Dr. Sabga was a volunteer for the Red Cross, the Community Foundation of Bloomington and Monroe County, and Volunteers in Medicine. She was a member of Congregation Beth Shalom, drummer in the band Don’t Call Me Betty and singer in the chorus Voces Novae. She was an avid cyclist, half and full marathoner, and triathlete; a talented maker of chocolates; a gardener; and a dedicated fan of the New York Yankees. She is survived by her husband Dan Melamed; her mother Patricia Sabga of Westlake, Ohio; her sisters Mardy of Kalamazoo, Michigan, and Patty of Malvern, England; her brothers Tom of Cincinnati and Mike of Westlake, Ohio; her nieces Sarah, Lesley and Robbie; and her nephews Art and Gabe. She was preceded in death by her father, Gabriel Sabga, MD.

BIRTH ANNOUNCEMENTS

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

Ada Lee Collins – 7 pounds, 7.5 ounces
July 15, 2011 (Stephen Collins, MD and Lucy)

Isaiah Matthew Silvestri – 6 pounds, 7 ounces
July 29, 2011 (Mark Silvestri, MD and Julie)

Matteo Curiale – 7 pounds, 1 ounce
August 19, 2011 (Jack and Darrah Curiale, MD)

Mariana Elena Phipps – 8 pounds, 4 ounces
November 3, 2011 (Michael Phipps and Madeline Dick-Biascochea, MD)
GRANTS AWARDED

Dr. Hugh Taylor – Pfizer – “Endometrial Effects of BZA – Prevention of Hyperplasia, Cancer and Endometriosis”

Dr. Vikki M. Abrahams – NIH/NICHD – “Innate Immune Responses of Trophoblasts in Pregnancy”

Dr. Emre Seli – Merck – “Identification and Characterization of Micro RNAs as Regulators of Maternal to Zygotic Transition”

Dr. Sabrina Diano – American Diabetes Association – “Role of Hypothalamic Prolyl Endopeptidase in Glucose Homeostasis”

Dr. Alessandro Santin – NIH/NCI – “CPE Peptide-Based Nanoparticle Therapy of Chemotherapy Resistant Ovarian Cancer”

Dr. Hugh Taylor – JB Pierce Lab Subaward NIH Funded – “Phytoestrogens, Insulin Resistance & Endothelial Function”


Dr. Nita Maihle – Susan G. Komen – “Evaluation of Novel Serum Biomarkers for Hispanic Women with Breast Cancer”

Dr. Alessandro Santin – The Honorable Tina Brozman Foundation – “Iron Oxide Nanoparticles Complexed to CPE Peptide for the Early Detection and Treatment of Chemotherapy Resistant Ovarian Cancer Stem Cells”

Dr. Divya Patel – Yale Cancer Center – “Oncological and Obstetric Outcomes of Excisional Treatment for Cervical Cancer Precursors in Reproductive Age Women”

Dr. Elisabeth Erekson – American Urogynecologic Society – “Frailty and Functional Status in Older Women with Urinary Incontinence”

Albert McKern Memorial Funds Recipients 2011:

Dr. Yingqun Huang – “Role of Activated Decidual Cells in Natural Killer Cell Recruitment and Preeclampsia”

Dr. Seth Guller – “Hofbauer Cell (HBC) Dysfunction in Preeclampsia”

Dr. Umit Kayisli – “The Impact of Coordinated Actions of Interleukin-6 and Interleukin-11 in the Regulation of Exaggerated Maternal Inflammatory Response in Preeclamptic and Chorioamnionitic Pregnan-cies”
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 Gynecologic Oncology (90.8)
- Yale Maternal-Fetal Medicine (90.5)
- Yale Reproductive Endocrinology (92.5)
- Yale Urogynecology (90.1)

YALE OB/GYN PHYSICIANS ON 2011 TOP DOCS LISTS

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

- Joshua Copel, MD (MFM)
- Charles J. Lockwood, MD (MFM)
- Pasquale Patrizio, MD (REI)
- Thomas Rutherford, MD (Gyn Oncology)

Closer to home, *Connecticut Magazine* identified six physicians as “Top Docs” in their 2011 annual survey:

- Michael R. Berman, MD (County Ob/Gyn Group PC)
- Ian M. Cohen, MD (Associated Women’s Health Specialists PC)
- Edmund F. Funai, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
- Charles J. Lockwood, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
- Norman A. Ravski, MD (County Ob/Gyn Group PC)
- Howard Simon, MD (County Ob/Gyn Group PC)

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

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

YNHH is the primary teaching hospital of Yale School of Medicine. Gynecology services at Yale-New Haven were ranked 16th by *U.S. News & World Report*.

Twelve Ob/Gyn doctors were selected based on a peer nomination process:

- Masoud Azodi, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, Gyn Oncology)
• Joshua Copel, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
• Emily Fine, MD (Gynecology Group)
• Charles J. Lockwood, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
• Vincent Lynch, MD (Greater New Haven Ob-Gyn Group PC)
• Urania Magriples, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
• Michael Paidas, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, MFM)
• Pasquale Patrizio, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, REI)
• Thomas J. Rutherford, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, Gyn Oncology)
• Alessandro Santin, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, Gyn Oncology)
• Peter E. Schwartz, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, Gyn Oncology)
• Hugh Taylor, MD (Yale Department of Obstetrics, Gynecology and Reproductive Sciences, REI)

NOTE: Doctors are listed in alphabetical order, and the results are not reflective of any rank order.

RECORD NUMBER OF ALUMNI IN PRESTIGIOUS POSITIONS

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

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

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

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

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

DID YOU KNOW?

Charles J. Lockwood, MD, accepted the position as Dean of The Ohio State University College of Medicine, Columbus, Ohio. Dr. Lockwood becomes the fifth Yale Ob/Gyn alumnus to secure a highly regarded position as dean at a medical school.

Peter E. Schwartz, MD, the John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences and Vice Chair, Gynecology, stepped in to serve as Interim Chair for the Department.

Edmund F. Funai, MD, has accepted the position as Associate Dean of The Ohio State University College of Medicine, Columbus, Ohio.

Catalin S. Buhimschi, MD, Associate Professor of Obstetrics and Gynecology, serves as Interim Section Chief for the Division of Maternal-Fetal Medicine and Interim Chief of Obstetrics at Yale-New Haven Hospital.

Stephen Thung, MD, has become Director of the Maternal-Fetal Medicine Practice of The Ohio State University College of Medicine, Columbus, Ohio.

Antonette T. Dulay, MD, Assistant Professor of Obstetrics and Gynecology, and Urania Magriples, MD, Associate Professor of Obstetrics and Gynecology, serve as Co-Directors of the Maternal-Fetal Medicine Division Clinical Practice.

Hugh S. Taylor, MD, received the 2011 Mentor of the Year Award, American College of Obstetricians and Gynecologists, as well as the 2012 Endometriosis Foundation of America Honoree of the Year. Dr. Taylor also served as the Postgraduate Program Director this year at ASRM and became the Chair Elect of the ASRM Endometriosis Special Interest Group. Additionally, Dr. Taylor was elected to Council, Society for Gynecologic Investigation.
Sonya S. Abdel-Razeq, MD, serves as Medical Director of the Maternal Special Care Unit at Yale-New Haven Hospital. Dr. Abdel-Razeq directs and coordinates the clinical activities related to antenatal management of a variety of high-risk maternal and fetal conditions on the Maternal Special Care Unit at YNHH.

Michelle Glasgow, MD, and Homa Khorrami, MD, were elected as the Administrative Chief Residents for the 2011-2012 academic year.

Lawrence K. Wartel, MD, stepped down as Associate Chief of Ob/Gyn at YNHH. He became the Associate Chief of Obstetrics and Gynecology at YNHH in 1987.

Steven Fleischman, MD, is the new Associate Chief of Ob/Gyn at YNHH. Dr. Fleischman represents the members of the Community attending staff and serves as a formal liaison between the Community, the University and the Hospital.

Fundraising. Discovery to Cure has received over $46,000 this year; over $15,000 was raised from the Fourth Annual Discovery to Cure Walk to benefit ovarian cancer research, which was held at Sherwood Island State Park in Westport, Connecticut, on September 18, 2011.

YNHH-HSR Merger. The boards of both hospitals have formally approved the merger. The next phase entails regulatory matters involving the State of Connecticut Attorney General and the Federal Trade Commission (FTC). This process can take up to 18 months (Cynthia Sparer/OB Council News, October 14, 2011 edition).

OB Safety Committee. YNHH had 4,396 deliveries in the most recent fiscal year. This is a 2.6% increase from the prior year. The cesarean section rate has decreased to 34.6% from 35.5% and breaks down as follows: MFM 48%, Community 34.8% and Women’s Center 25.6% (presented by Dr. Chris Pettker/OB Council News, October 14, 2011 edition).

Out & About. On September 18, 2011, students and faculty brought their competitive spirit to Yale’s Cullman-Heyman Tennis Center for the Student/Faculty Tennis Classic. Pasquale Patrizio, MD, joined in the spirited match.

FACULTY PROMOTIONS EFFECTIVE JULY 1, 2011:

Mert Bahtiyar, MD, to rank of Associate Professor, Clinician Educator Track
Jessica Illuzzi, MD, to rank of Associate Professor, Clinician Educator Track
Michael Paidas, MD, to rank of Professor, Clinician Educator Track
Thomas Rutherford, MD, to rank of Professor, Clinician Educator Track
Stephen Thung, MD, to rank of Associate Professor, Clinician Educator Track

VOLUNTARY FACULTY PROMOTIONS EFFECTIVE JULY 1, 2011:

Harold Sauer, MD, to rank of Clinical Professor

VOLUNTARY FACULTY NEW APPOINTMENTS EFFECTIVE JULY 1, 2011:

Yoni Barnhard, MD, to rank of Associate Clinical Professor
Peter Marcus, MD, to rank of Associate Clinical Professor
Lyree Mikhail, MD, to rank of Associate Clinical Professor
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.

BLOGS

Yale Fertility Center Blog: http://yalefertilitycenter.blogspot.com/

Yale Reproductive Endocrinology Blog: http://yalereproductiveendocrinology.blogspot.com/

FACEBOOK PAGES

Yale RE: http://www.facebook.com/pages/Yale-Reproductive-Endocrinology/68087952760

YFC: http://www.facebook.com/pages/Yale-Fertility-Center/55523238825?ref=ts


Yale Program for Menopause: http://www.facebook.com/pages/Yale-Menopause-Program/77498424812

Yale Program for In vitro Fertilization: http://www.facebook.com/pages/Yale-In-Vitro-Fertilization-Program/88633862352


Yale Program for Reproductive Endocrinology: 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
Yale School of Medicine
Box 7611
New Haven, CT  06519-0611

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

DONATIONS

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

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

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

Name:
Institution:
Street:
City: State: Zip:
Country:
Donation Amount:
WE WANT TO SHARE YOUR SUCCESSES!

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

Name:  
Year:  
Street:  
City:  
State:  
Zip:  
Country:  
☐ Check if this is a new address

Tel:  
Fax:  
Email:  

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

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

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

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

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

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

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

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

Amount Paid: _________________________________
Date: _________________________________

Retain this portion for your records

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**YOGS MEMBERSHIP INVOICE**

<table>
<thead>
<tr>
<th>Name (Last)</th>
<th>(First)</th>
<th>(Middle Initial)</th>
<th>(Degree)</th>
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</thead>
</table>

Institution/Practice Name

Street Address

Office/Suite #

City

State/Province

Zip/Postal Code

Country

Phone (_____) ______________________________

Email Address __________________________________

Spouse/Partner’s Name _______________________________________________________________________

**Membership Dues** (please check one)

☐ One Year $150

☐ Two Years $200

☐ Lifetime Membership $1,500

**Two ways to pay:**


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