Research Presentation 2007

Abstracts

Presenting Residents

Kristen Cotter, MD

Risk of high-grade cervical neoplasia in HIV-infected women with mildly abnormal cervical cytology.

K. Cotter MD, MPH; P. Hirway, MS; S. Cu-Uvin MD; L. Boardman MD ScM

Objective: The goal of this study was to evaluate histologic outcomes, in particular high-grade cervical intraepithelial neoplasia (CIN 2 or worse), among a cohort of HIV (Human Immunodeficiency Virus) -positive and HIV-negative women with mildly abnormal cervical cytology.

Methods: This is an age-matched cohort study using a colposcopic database of 3013 women who underwent colposcopy between August 1999 and May 2006. Data collected included demographic information, Pap screening results, colposcopic impression and biopsy results. Descriptive statistics and crude and adjusted odds ratios with 95% confidence intervals were calculated.

Results: Of the 103 HIV-infected women seen for the evaluation of abnormal cervical cytology, 80 (78%) had ASC-US (atypical squamous cells of undetermined significance) or LSIL (low-grade squamous intraepithelial lesions) on referral cytology. Age-matched controls included 322 HIV-negative women with mildly abnormal cervical cytology. Compared to HIV-negative women, HIV-infected women were significantly more likely to be smokers, to report a history of sexually transmitted infections, and to be younger at time of first intercourse. HIV-positive women were as likely as HIV-negative women to have CIN 2+ on biopsy (7 or 9% of HIV+ women and 29 or 9% of HIV-negative women had CIN 2+; crude OR 0.97, 95% CI 0.41-2.30). Following adjustment for smoking, sexually transmitted disease history, age at first coitus and number of lifetime sexual partners, the odds of CIN 2+ in HIV-infected women rose slightly, but not significantly (adjusted OR 1.19, 95% CI 0.43-3.3). In the HIV-infected cohort, histologic high grade disease was more commonly found among women with CD4 counts <200 (43%) compared to women with CD4 counts ≥200 (9%, OR 7.5, 95% CI 0.93 to 60.43).

Conclusion: High-grade disease was encountered in 9% of patients, irrespective of HIV status, with ASC-US or LSIL. Worsening immunosuppression in the HIV-infected population was, however, associated with the finding of CIN 2+.

Kelly Fogleman, MD

Two hour versus four hour monitoring in obstetrical patients following a trauma.

K. F. Fogleman, MD; M. Paglia, MD; M. Phipps, MD; S. Weitzen, PhD; F. Lozowski; C. Raker.

Objectives: Trauma complicates one in every twelve pregnancies. When a pregnant woman with a viable fetus experiences some type of trauma, she is usually monitored for 4 hours. The goal of monitoring is to evaluate for signs of potential placental abruption and fetal compromise. It is uncertain whether such a prolonged duration of monitoring is necessary.

Methods: We conducted a retrospective cohort chart review of women with singleton pregnancies greater than 24 weeks gestation presenting to an obstetric triage unit after experiencing some type of trauma. Data abstracted from the charts included basic demographic information, specific details of the trauma, clinical presentation to and disposition from the triage unit as well as information from the eventual delivery. An investigator who was blinded to the disposition from the triage unit separately reviewed the first 2 hours of cardiotocographic monitoring that occurred. From this review, a decision was made as to whether the
patient should be admitted for further monitoring versus being discharged home. The disposition
decision made by the reviewer was compared with the actual disposition decision made at the time of presentation.
We hypothesize that the decision to admit patients for further monitoring can be made after 2 hours of
cardiocotographic monitoring with the same accuracy as 4 hours of monitoring.
RESULTS: During the time period 9/1/04 through 6/17/06, 478 patients that met criteria were seen in the
triage unit. Of these women, 118 were admitted. Further results regarding the comparison with the
reviewer’s evaluation will be presented on Resident Research Day
CONCLUSIONS: Pending.

Stacey Lievense, MD
Intrapartum Group B Streptococci prophylaxis in patients who report a penicillin allergy.
S. P. Lievense, MD; K. A. Matteson, MD, MPH; B. Cantazarro, BS.
OBJECTIVE: To examine provider adherence to the 2002 CDC guidelines for Group B Streptococci
(GBS) prophylaxis in patients who reported a penicillin allergy.
METHODS: This is an IRB approved retrospective cohort study of 266 GBS positive, penicillin (PCN)
alлерgic obstetric patients who delivered at our institution between January 2004 and December 2005.
Medical records were analyzed for type of delivery, gestational age at delivery, means of documenting the
GBS positivity (urine bacteruria, screening culture), antimicrobial sensitivity testing, and antibiotics
administered. Women who delivered between January and March 2004, women with a planned cesarean
section, and women with a delivery prior to 37 completed weeks were excluded from the analyses of
microbial sensitivity testing and appropriate antibiotic administration. Additionally, women who were
determined to be low risk for anaphylaxis and thus received a cephalosporin were excluded from analyses of
antimicrobial sensitivity testing. Appropriate antibiotic was defined as a cephalosporin for patients at low
risk for anaphylaxis, clindamycin or erythromycin if GBS was susceptible to both of these antibiotics, and
vancomycin if antimicrobial sensitivity was unknown or if GBS was resistant to either clindamycin or
erythromycin. Data were analyzed using STATA, v. 9.0. Chi squared and t-test were used where appropriate.
Pearson’s correlation was performed to determine if antimicrobial sensitivity testing and administration of an
appropriate antibiotic improved over time.
RESULTS: Ninety-five percent of GBS positive, PCN allergic women received antibiotic prophylaxis and
the majority received clindamycin (83%). Antimicrobial testing was performed in only 12% of patients and
there was no change in testing over time (r=-0.062, 95%C1 -0.48 to +0.38). Women who received
clindamycin were more likely to have unknown antimicrobial susceptibilities than those that received
vancomycin (91% vs 55%, p=0.01). Only 17% of patients received an appropriate antibiotic. More women
received an appropriate antibiotic in 2005 than in 2004 (20% vs. 11%, p=0.09). However, this increase in
appropriate antibiotic over time was not statistically significant (r=0.35, 95%C1 -0.09 to +0.68).
CONCLUSIONS: Adherence to the 2002 CDC Guidelines for GBS prophylaxis in PCN allergic women is
suboptimal. Significant improvements are necessary in obtaining antimicrobial sensitivity testing and choosing an appropriate antibiotic for GBS positive women with a reported penicillin allergy.

Jessica Salak, MD
Career aspirations and pregnancy intentions in pregnant teens.
J. R. Salak, MD; M. G. Phipps, MD, MPH; S. Weitzen, PhD; C. Rosengard, PhD, MPH
OBJECTIVE: Educational achievement for teen mothers overall is low; however, it is unclear whether
pregnant teens have career aspirations that require educational achievement beyond high school and how
pregnancy intention may be related to these aspirations. Understanding this relationship may help target interventions for pregnancy prevention as well as programs to encourage school achievement for pregnant and parenting teens. This study aims to investigate the association between career aspirations of pregnant teens who are continuing their pregnancies and pregnancy intention.

METHODS: This study includes 261 pregnant adolescents (12-19 years old) who presented for their first prenatal visit from March 2002 through February 2005 (IRB approval December 2001). Adolescents were consented and participated in a 30-minute interview as part of a larger cohort study addressing pregnancy attitudes and outcomes. Pregnancy intention was assessed with responses to the question “When did you want to be pregnant?” with responses of “more than a year from now” and “did not want to be pregnant” representing an unintended pregnancy. The outcome for our analysis included categorizing qualitative responses to the question “What kind of work do you hope to do in the future?” into three categories: less than college (requiring less than a college education), college or more (requiring at least a college education) and undecided. Demographic variables and school plans were used to characterize the sample. The analysis included chi-square, and Fisher’s exact test.

RESULTS: The study population included 20% (n=53) 12-15 year olds, 38% (n=100) 16-17 year olds and 41% (n=108) 18-19 year olds. Overall, 76% (n=199) of the adolescents reported their pregnancies were unintended. 59% (n=153) reported a career that required at least a college education, 29% (n=75) reported a career that requires less than a college education and 12% (n=33) were undecided. Career aspirations that would require at least a college education were reported by 58% (n=116) of those who reported unintended pregnancy and 63% (n=37) of those who reported intended pregnancy (p-value =0.54). Seventy-two percent (n=53) of those adolescents who had finished high school and 68% (n=208) of those who had not finished high school reported they wanted to go back to school right after having the baby.

CONCLUSION: The majority of teens in this study reported their pregnancy was unintended, had career aspirations requiring at least a college education and planned to go back to school after the baby was born. There was no difference in career aspiration between the proportion of teens who reported their pregnancy was intended versus unintended. Teen pregnancy prevention programs may want to focus on helping at-risk teens understand what educational levels are required to achieve their career aspirations. For teens that become pregnant and choose to continue their pregnancy, addressing their career aspirations may help teen mothers achieve their educational goals.

Mary Christina Simpson, MD

Comparison of frozen section to final pathology for low malignant potential tumors of the ovary.

Preceptor: Richard Moore, MD

OBJECTIVE: To determine the accuracy of frozen section diagnosis for low malignant ovarian tumors (LMP) compared to final pathology results. To evaluate surgical staging of mucinous and serous subtypes of LMP ovarian tumors.

METHODS: This was an IRB approved retrospective chart review. The WIH pathology database was queried for all diagnoses of LMP ovarian tumors between 1992-2005. Fisher’s exact test was used to compare frozen section to final pathology and staging frequency by type of surgeon and tertiary care (WIH) versus community hospital (CH).

RESULTS: 242 LMP tumors of the ovaries were identified from 1992-2005. There were 159 (WIH=91, CH=68) serous LMP and 83 (WIH=49, CH=34) mucinous LMP ovarian tumors.

The median age for all serous LMP tumors was 47 years (range 18 to 87). There were 73 serous LMP ovarian tumors diagnosed on frozen section with 7 cases upgraded to invasive carcinoma on final pathology.
for a sensitivity of 90.4% (95% CI: 81.2-96.1%). At CH, 38 serous LMP were diagnosed on frozen section, 4 cases were upgraded to an invasive malignancy for a sensitivity of 89.5% (95% CI: 75.2-97.1%). For cases at WIH, Gyn oncologist staged or partially staged 88.2% (95% CI: 76.1-95.6%) and Gynecologist staged or partially staged 61.5% (95% CI: 40.6-79.8%) (p=0.009). Cases at CH, Gyn oncologist staged or partially staged 78.6% (95% CI: 49.2-95.3%) and Gynecologist staged or partially staged 48.5% (95% CI: 30.8-66.5%) (p=0.1). The distribution of all staged serous LMP tumors was 29 Stage I, 0 Stage II, 15 Stage III and 0 Stage IV.

The median age for all mucinous LMP tumors was 45 years (range 18 to 87). There were 25 mucinous LMP ovarian tumors diagnosed on frozen section with 6 cases being upgraded on final pathology for a sensitivity of 76.0% (95% CI: 54.9-90.6%). At CH, 17 mucinous LMP ovarian tumors were diagnosed on frozen section with 1 case being upgraded to a malignancy giving a sensitivity of 94.1% (95% CI: 71.3-99.9%). For cases at WIH, Gyn oncologist staged 60.0% (95% CI: 36.1-80.9%) and Gynecologist staged 60.0% (95% CI: 14.7-94.7%). For cases at CH, no patients were staged for mucinous LMP tumors. For all mucinous tumors that were completely staged there were 21 Stage I and only 1 Stage III.

CONCLUSION: Frozen pathology is an accurate predictor of final pathology in both tertiary care center and in community hospitals. The percent of LMP tumors staged by Gyn-oncologists is significantly higher than the percent by Gynecologists for serous and mucinous tumors at WIH, however this difference does not hold true for community hospitals. Mucinous tumors were rarely upgraded and therefore staging may not be necessary.

Roxanne Vrees, MD

Characteristics and outcomes of women with endometriosis associated ovarian and extra-ovarian cancers.

Preceptor: Don Dizon, MD; Carolyn McCourt, MD

OBJECTIVE: Although there is a well-documented association between endometriosis and malignancy, a true cause-and-effect relationship remains controversial. Previous studies have established endometriosis associated malignancies as a distinct entity, yet few have examined the course and response to treatment of these women’s disease with that of other women with ovarian cancer. Our aim was to review the experience with endometriosis associated ovarian and extra-ovarian cancers at the Program in Women’s Oncology.

METHODS: In this retrospective cohort study, patients were identified through the Department of Pathology database who had a concomitant diagnosis of ovarian or peritoneal cancer and endometriosis on their surgical specimen between 1991-2005. Medical records were analyzed for demographic and medical information, stage of disease, histology, relationship with endometriosis, CA-125 levels, treatment protocols, response to therapy, recurrence, and follow-up data. Women with secondary malignancies within five years of diagnosis or those with synchronous primary malignancies were excluded from analyses.

RESULTS: Of 89 patients identified, we have collected follow-up data thus far for twenty-seven patients (30%). One patient was excluded from subsequent statistical analysis due to an unknown primary site. Of the remaining 26 patients, the median age at surgery was 51 years. Endometrioid adenocarcinoma was the most common histologic type (46%), followed by mixed histology (23%), serous (19%), and clear cell adenocarcinoma (12%). Seven (27%) cancers appeared to arise in endometriosis, while 12 (46%) had endometriosis in the same location as the primary tumor, and 7 (27%) had incidental endometriosis on pathologic report. Twenty five women (96%) were completely staged as Stage I in 11 (42%) Stage II in 6 (23%), Stage III in 7 (27%) and Stage IV in 1 (4%). Optimal cytoreduction was achieved in 23 (88%). Postoperatively, 20 (77%) women received adjuvant cytotoxic chemotherapy, while 4 (15%) received no further therapy. During a median follow-up of 35.5 months (range 3.3-124.5) four recurrences were
documented. Seventeen of the 26 women (71%) were alive without evidence of disease, four (17%) women had succumbed to their disease, one (4%) was alive with disease, and two (8%) were deceased due to intercurrent disease. Compared to contemporary statistics regarding ovarian cancer, it appears that this indeed represents a distinct clinical entity from epithelial ovarian cancer where the median age at diagnosis is 63 years, between 60-70% of women present at an advanced stage (i.e. III to IV), and the major histologic type is serous adenocarcinoma.

CONCLUSION: Our preliminary analysis suggests that endometriosis associated ovarian cancer represents a distinct clinical entity, with an overall earlier age at diagnosis and improved overall survival. Survival rates, however, are closely related to stage of disease, and we are currently pursuing a matched control group to compare survival rates stratified by stage. Ongoing identification of cases also continues.

Presenting Fellows

Jennifer Ballard-Dwan, MD

Provider differences in violence documentation: A comparison with toxoplasmosis risk screening.

J. Ballard Dwan, MD; Yang Long

OBJECTIVE: Intimate partner violence occurs in approximately 4?8% of pregnancies. Despite the American College of Obstetricians and Gynecologists (ACOG) recommendations for routine screening and multiple prenatal visit opportunities, intimate partner violence screening occurs infrequently. Risks for less common conditions such as toxoplasmosis (incidence 0.0001%) are frequently screened. To increase awareness of this disparity, we evaluated documentation frequency for intimate partner violence as compared with toxoplasmosis risk factors.

METHODS: Using a dataset from 324 randomly selected women, we estimated the frequency of intimate partner violence and household cat exposure documentation and collected demographic information. Odds ratios and Fisher exact tests were used for bivariate statistical analysis. Public (resident and community health centers? PUB) and private practice (PRI) provider subgroup analyses were performed.

RESULTS: Fifty-two (16%) women were screened for intimate partner violence, with 8/52 (15%) screening positive. More PUB women were screened than PRI women (odds ratio [OR] 16.2, 95% confidence interval [CI] 8.1, 32.7). Significantly more PRI women had IPV documented when Hispanic, publicly insured, or when Chlamydia positive. Women in the PUB group did not display documentation differences between subgroups. Cat exposure prevalence was 47/219 (22%). Cat exposure documentation occurred in 219 (68%) women. Fewer PUB clinic attendees had cat exposure documentation (OR 0.31, 95%CI 0.18, 0.52). Women in the PRI group were 13 times more likely to be screened for cat exposure than for intimate partner violence (74 % vs. 6%), while there was no significant difference in the PUB group.

CONCLUSION: In our population, more documentation of toxoplasmosis risk occurs than for intimate partner violence, particularly in private clinics. Given the high prevalence of intimate partner violence in pregnancy, improved screening methods and documentation would increase the number of affected women identified.

Antonella Restivo, MD

Antiproliferative effect of mimosine in ovarian cancer.

M. Restivo, MD; L. Brard, MD; C.O. Granai, MD; N. Swamy MD

OBJECTIVE: Iron plays a critical role in cell proliferation and survival making it a potential target for
cancer therapy. Iron chelators have been shown to possess selective anti-neoplastic properties. Mimosine, a naturally occurring plant amino acid, acts as a potent iron chelator. Its use in gynecologic malignancies has yet to be tested. It works by arresting cell-cycle progression at the G1-S interface. The objective of our study was to evaluate the anti-proliferative effects of mimosine on human and rat ovarian cancer cells.

**METHODS:** Human (CaOV-3 & OvCAR) and rat (NuTu 19) ovarian cancer cell lines were treated for 24-72 hours with mimosine at doses ranging from 50 to 800 µM concentrations. Untreated cells were used as a control. Cell viability was measured by MTS reduction assay and cell proliferation was determined by BrdU incorporation. Apoptosis was analyzed by DNA fragmentation. Iron challenge studies were performed to determine the role of iron in the cytotoxic effect of mimosine.

**RESULTS:** Mimosine demonstrated dose-dependent anti-proliferative effects on all ovarian cancer cells tested. Cell viability was inhibited 70% at a dose of 200µM. Mimosine also inhibited DNA synthesis as revealed by BrdU incorporation assay. Fifty percent inhibition of DNA synthesis was observed at a dose of 100µM. This inhibitory effect of mimosine was reversed with the addition of ferric ion, indicating that the effect of mimosine is mediated by iron chelation. Mimosine also induces apoptosis as evident by fragmentation of nuclear DNA. Further analysis revealed involvement of caspases. Caspase 3 and 9 were activated with time when treated with Mimosine. However, caspase 8 was not activated indicating that the apoptotic extrinsic pathway is not involved. Analysis of survival signaling pathways revealed that Mimosine decreased activation of ERK 1/2 and AKT while, increasing the apoptotic signal p38 MAPK

**Conclusions:** Mimosine, a potent iron chelator, has cytotoxic and anti-proliferative effects on human and rat ovarian cancer cell lines. The cytotoxic effect of Mimosine is mediated by iron chelation with involvement of apoptosis. Mimosine induces apoptosis via the intrinsic, caspase 9 mediated pathway, while bypassing the extrinsic, caspase 8 mediated mechanism. Apoptosis was mediated by p38 MAPK activation, while survival signaling, ERK 1/2 and AKT, was suppressed. Mimosine, a naturally occurring amino acid has been shown to have a longer half-life and affordable cost making an attractive alternative therapeutic agent in the fight against ovarian cancer.

**Alvie C. Richardson, MD**

**Diminished production of interleukin-10 in gravidas with gestational diabetes mellitus.**

**Preceptors:** S. Sharma, MBBS, PhD; M. W. Carpenter, MD

**OBJECTIVE:** Pro-inflammatory cytokine, TNF-α, and anti-inflammatory cytokine IL-10 are produced by cells of the immune system as well as adipose tissue. TNF-α induces the production of IL-10 which in turn feeds back to inhibit TNF-α production. An inability to produce sufficient amounts of IL-10 predisposes to the effects of TNF-α, one of which is to impart insulin resistance. Gravidas with gestational diabetes mellitus (GDM) possess marked insulin resistance and are commonly obese. The purpose of this study was two fold. First to compare serum concentrations of TNF-α and IL-10 between gravidas with and without GDM, and second to compare TNF-α and IL-10 production capability of circulating immune cells between these two groups. We hypothesized that gravidas with GDM display an IL-10 deficiency characterized by decreased serum concentrations of IL-10 as well as diminished IL-10 production capability of circulating immune cells.

**METHOD:** This case-control study examined 8 insulin-treated GDM and 8 non-diabetic non-laboring gravidas enrolled at 35-38 weeks gestational age. Ethnicity, EGA, and body mass index (BMI) were recorded at time of blood draw. Peripheral blood mononuclear cells (PBMCs) were obtained from 6 with and 4 without GDM. Serum concentrations of TNF-α and IL-10 were measured from serum and in supernatant from PBMC culture stimulated for 24 hours with lipopolysaccharide (LPS), phorbol myristate acetate (PMA)-ionomycin, mannose, and varying concentrations of glucose. Cytokine concentrations were
determined using Bioplex immunoassay. Data were log transformation to achieve normal distribution as necessary. Student’s t-test was used to determine statistical significance.

RESULTS: Gravidas with GDM had a significantly lower mean log concentration of serum IL-10 (0.94 pg/ml vs. 1.56 pg/ml, p=0.004) as well as LPS stimulated PBMC concentrations of IL-10 (4859 pg/ml vs. 7664 pg/ml, p=0.02) than non-GDM gravidas. No group differences of TNF-α concentrations, ethnicity, EGA, or BMI at time of blood draw were identified. To test the independent contribution of fat mass and glucose intolerance to serum cytokine concentrations, we also performed a simple regression analysis of BMI and GDM on serum IL-10 concentration demonstrating that GDM remained associated with IL-10 level, independent of BMI.

CONCLUSION: Glucose intolerance in late pregnancy is associated with lower levels of IL-10 expression. This lower serum concentration may reflect decreased production by peripheral blood mononuclear cells. The association between glucose intolerance and decreased IL-10 concentration appears to be independent of fat mass as reflected in late pregnancy body mass index. This small study could not identify differences in TNF-α concentrations or production capacity and did not address the effects of or metabolism/clearance of measured cytokines. This study suggests that the interaction of maternal metabolic state, fat mass and anti-inflammatory homeostasis requires further exploration.

Katerina Tsiapali, MD
Clinical evaluation of the axilla as a predictor of the presence of nodal disease in breast cancer patients that have received neoadjuvant chemotherapy.
E. Tsiapali, MD; D. Dizon, MD, FACP; L. Le, BA; P. Barlow, NP; M. Steinhoff, MD; W. Sikov, MD; J. Gass, MD.

OBJECTIVES: Patients with locally advanced breast cancer (LABC) who receive neoadjuvant chemotherapy (NAC) often have abnormal palpable nodes during surgical exploration. We aim to determine how accurately intraoperative nodal evaluation predicts axillary metastatic disease following NAC.

METHODS: We retrospectively reviewed the charts of 41 patients with LABC treated with NAC on the BrUOG-95 study and compared the intraoperative nodal descriptions with the final pathologic findings.

RESULTS: 29 of 41 cases met criteria for analysis. In 16/29 (55.2%) operative reports the axillary nodes were described as suspicious for harboring metastatic disease. 10 of these patients (62%) had nodal metastases on pathologic examination but the remaining 6 (38%) had negative nodes. The sensitivity of clinical exam was 58% and the specificity 50%.

CONCLUSIONS: In our series intraoperative clinical evaluation of the axilla in patients with LABC treated with NAC was accurate in predicting the presence of nodal metastases in 55% of cases.