Presenting Residents

Gema E. Fernandez, MD

Contraception: knowledge, lifestyles, and behaviors.
G.E. Fernandez, MD; M. Phipps, MD, MPH; R. Shackelton; F. Lozowski; A. Meers.

Objective: Efforts to make ECP available over the counter have been unsuccessful to date for many reasons, including claims that ECP encourages irresponsible sexual behavior and will increase rates of sexually transmitted diseases. This study looks at whether there are differences between women seeking ECP and women seeking general family planning services in lifestyle and sexual behaviors as well as differences in knowledge about ECP and contraception in general.

Methods: This cross-sectional study performed during August 2003 through March 2004 included a total of 245 women. A group of 128 women presenting to the Women & Infants Hospital Triage Unit seeking emergency contraception (ECP group) and 117 women presenting to the Women’s Primary Care Center Family Planning Unit for contraceptive counseling (WPCC group) were asked to complete a self-administered anonymous questionnaire which included demographic information, medical and sexual history, and questions regarding contraceptive knowledge. Comparisons between the groups included contraceptive use, history of STD’s, and number of sexual partners, as well as comparisons in knowledge about ECP and other contraceptives.

Results: Comparing the ECP and WPCC groups, there were no significant differences in educational levels. Although there was no difference found between the two groups regarding the presence of STD’s in the past six months (2% ECP group vs. 6% WPCC group, p=0.38), the ECP group had a lower overall proportion of STD’s as compared with the WPCC group (17% vs. 44%, p<0.01). As for contraception, 78% of the WPCC group used some form of contraception with the last episode of intercourse, of which 73% used OCP’s. Only 56% of the ECP used contraception with the last episode of intercourse, of which 83% used condoms. There was a significantly higher number of sexual partners within the past 6 months in the ECP group (1.69 vs. 0.95, p<0.01); over the course of a lifetime the ECP group averaged 5.6 partners and the WPCC group averaged 4.2 partners (p=0.054). The groups did not differ in the number of episodes of unprotected intercourse. Overall knowledge for many questions about contraception was similar. For example, a question about tubal ligation offering STD protection was answered correctly (“false”) by 88% of the ECP group and 95% of the WPCC group, and a question about OCP’s causing ovarian cancer was answered as “unsure” by 49% of the ECP group and 50% of the WPCC group. In contrast, more women in the ECP group reported knowledge about the existence of emergency contraception as compared with the WPCC group (84% vs. 53%, p<0.01). As for knowledge about ECP availability in the subgroup of women who reported knowing about the existence of ECP, only 44% in each group knew it was available with a prescription.

Conclusion: This study does not support the idea that women seeking ECP have significantly increased rates of sexually transmitted diseases or risky sexual behavior. Overall, women in our study had limited knowledge regarding contraception in general and emergency contraception specifically. This study underscores the need for effective contraceptive education including information about emergency contraception for all women. As practitioners, we need to be sensitive to the needs of our patients and move towards making ECP more widely available and accessible to all women.
Evelyn L. Fleming, MD

Does body mass index predict cutaneous reactions to pegylated liposomal doxorubicin?
E.L. Fleming, MD; D.S. Dizon, MD; P.A. DiSilvestro, MD; R.G. Moore, MD; C. Granai, MD; M.E. Gordinier, MD.

Objective: The dose limiting toxicity of pegylated liposomal doxorubicin (PLD) is palmar-plantar erythrodysesthesia (PPE). Some physicians may have a bias against using this drug in overweight patients, postulating that larger size increases the likelihood of drug deposition that may predispose to PPE. The aim of this study was to determine whether the body mass index (BMI) predicted frequency or severity of cutaneous reactions in patients receiving PLD.

Methods: The records of all patients receiving PLD for a gynecologic malignancy between 1996 and 2003 were reviewed. Chemotherapy history, BMI at the start of PLD treatment, dose, infusion time, and adverse effects were all collected. In addition, type and grade of skin reactions and treatment for them were extracted. Finally, history of potential predisposing factors was recorded, such as sun exposure, medical conditions, and allergies. The reason for drug discontinuation was also ascertained.

Results: 103 patients were included in this analysis. 429 cycles of PLD were given with a median of 4 cycles per patient. The primary toxicity was skin reaction, with 36% experiencing PPE. Of those with PPE, 54% had Gr1 reactions, 32% had Gr2 reactions, and 14% had Gr3 reactions. There were no Gr4 reactions. The mean BMI in patients who had clinically significant skin reactions was identical to those who did not, 29 vs. 28.8, respectively. When patients were analyzed by subsets of weight, the incidence of skin reactions among patients of different weight groups was similar. Logistic regression revealed no relationship between BMI and grade of rash. None of the potential predisposing factors analyzed correlated with an increased incidence of cutaneous toxicity.

Conclusion: Increased BMI is not associated with an increased risk of skin reactions or PPE. Among the patients treated with PLD, the rate of skin toxicity was 36% and was a major reason for discontinuing the drug. Further work is required to better define which of our patients are at risk for PPE.

Ernest Han, MD, PhD

Impact of serous histology on survival in patients with mixed serous and endometrioid endometrial cancers.
E. Han, MD, PhD; T. Tejada-Berges, MD; R. Quddus, MD; S. Weitzen, MD; M. Gordinier, MD.

Objective: Uterine papillary serous carcinoma (UPSC) represents an aggressive histological subtype of endometrial cancer, with poor 5-year survival rates, compared with endometrioid subtype. Several reports suggest that endometrial cancer patients with mixed histological subtypes, containing at least 25% UPSC, have similar poor survival outcomes as compared to patients with pure UPSC subtype. To test this hypothesis, we compared the overall survival among patients with pure grade 3 endometrioid, various mixtures of endometrioid and UPSC, and pure serous histological subtypes.

Methods: Patient information was obtained from the Program in Women’s Oncology and Tumor Registry from 1990-2000. We included patients that were fully staged according to the 1988 FIGO staging criteria. We excluded those patients with synchronous primary tumors and other aggressive histological subtypes (e.g., clear cell). Demographic information and overall survival data were obtained from 41 patients with grade 3 endometrioid, 20 patients with pure UPSC, and 26 patients with mixed endometrioid and UPSC histological subtypes.

Results: For the UPSC and mixed subtypes, there were 14 with stage I disease, 6 with stage II disease, 12 with stage III disease, and 14 with stage IV disease. For grade 3 endometrioid subtypes, there were 19 with stage I disease, 5 with stage II, and 14 with stage III, and 3 with
stage IV. The overall survival data for pure serous, pure endometrioid and mixed subtypes are under statistical review at this time.

**Conclusion:** We anticipate that the results from this study may have important clinical implications in the treatment of patients with mixed endometrial cancers, especially those patients with a small percentage of UPSC subtype.

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**Katina Robison, MD**

*Inguinal sentinel node dissection versus standard inguinal node dissection in patients with vulvar cancer: a comparison of the size of metastasis detected in inguinal lymph nodes.*

K. Robison, MD; R.G. Moore, MD; C.O. Granai, MD; L. Brard, MD, PhD; W. Gajewski, MD; M. Gordinier, MD; M.M. Steinhoff, MD.

**Objective:** The emergence of sentinel lymph node (SLN) technology has provided the ability for an increased pathologic evaluation for lymph node metastasis through the use of ultra-staging. The SLN has been shown to be predictive of the metastatic status of its nodal basin. More recently, SLN dissections have been employed in the evaluation of the inguinal lymphatic basins in patients with vulvar malignancies. We hypothesize the average size of metastasis detected in non-palpable inguinal lymph nodes is smaller when detected through the use of SLN dissection and ultra-staging versus complete inguinal node dissection (CND).

**Methods:** This was an IRB-approved, retrospective study. The tumor registry database was searched to identify all patients diagnosed with a vulvar malignancy from 1990 to 2003. The records were reviewed to identify patients with inguinal lymph node metastasis. Only patients with non-palpable inguinal lymph nodes (metastasis 1 cm or less) were included in the analysis. All pathology slides were reviewed. The smallest metastatic foci of cells were measured from lymph nodes obtained through CND and compared with the largest metastatic foci of cells detected in SLN. The mean size and standard deviation for each group were calculated and analyzed with a 2-sample t-test.

**Results:** There were 317 patients identified with a vulvar malignancy. SLN dissections were performed in 37 cases and CND in 280 cases. Fifty-eight patients were found to have metastatic disease to the inguinal lymph nodes. Thirty of these patients had no evidence of lymph node metastasis on clinical exam or at the time of their EUA. There were 7 patients with metastasis detected through a SLN and 23 patients through a CND. The mean size of the metastatic foci detected in the SLN group was 2.52 mm (std. dev. 1.55), and in the CND group was 4.35 mm (std. dev 2.63). This was statistically significant (P=0.036: 95% CI [-3.513, -0.124]).

**Conclusion:** SLN dissection with ultra-staging allows for a more extensive pathologic examination of lymph, nodes and may allow for the detection of smaller tumor foci than when a CND is performed. The clinical implication of the detection of these metastases remains to be determined.

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**Kathleen M. Schmeler, MD**

*Evaluation of 61 persistent adnexal masses in pregnancy.*

K.M. Schmeler, MD; W.W. Mayo-Smith, MD; J.F. Peipert, MD; R. Shackelton, MD; C.O. Granai, MD; M.E. Gordinier, MD.

**Objective:** To review the outcome of patients with adnexal masses greater than 5 cm in diameter, persisting beyond 16 weeks gestation.

**Methods:** A retrospective review was performed of patients diagnosed with adnexal masses during pregnancy between 1990 and 2003 at Women & Infants Hospital of Rhode Island. Data collected included age, gravity/parity, gestational age at diagnosis, symptoms, and physical exam findings. Ultrasounds were reviewed for lesion size, presence of solid components, septations,
and anatomic site. The masses were scored on a 5-point scale for risk of malignancy by radiologists with extensive experience in gynecological imaging. Patients managed with antepartum surgery were compared with those who underwent close observation. Maternal and fetal outcomes, complications and surgical pathology were reviewed.

**Results:** 127,177 deliveries were performed at our institution between 1991 and 2003. 61 patients (0.048%) were found to have persistent adnexal masses greater than 5 cm in diameter. Mean gestational age at diagnosis was 19.1 weeks. The majority of masses were mature teratomas (41%), followed by functional cysts (15%). Two malignancies were diagnosed (3.3% of masses, 0.0016% of deliveries). Average mass size was 14.3 cm for the malignancies, versus 7.7 cm for the benign tumors (P<0.01). Fifteen patients (24.6%) underwent antepartum surgery, with five patients (8.2%) requiring emergent surgery secondary to suspected torsion. Mean gestational age at delivery was 38.8 weeks. There were no clinically significant differences in maternal or fetal outcome between patients undergoing antepartum surgery versus close observation during pregnancy.

**Conclusion:** Although the prevalence of adnexal masses in pregnancy is high, ovarian malignancy in this population is rare. Careful radiology review to identify masses concerning for malignancy is an important part of the evaluation. Close observation is a reasonable alternative to antepartum surgery in select patients with persistent adnexal masses during pregnancy.

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**Cara Stanko, MD**

**Triage of ASC-US: evaluating the need for HPV testing in adolescents.**

C. Stanko, MD; S. Weitzen, PhD; C.J. Sung, MD; L.A. Boardman, MD, ScM.

**Objective:** To determine age-stratified prevalence of oncogenic HPV infection and to evaluate traditional risk factors for HPV acquisition among a cohort of women with ASC-US smears.

**Study Design:** This was a retrospective chart review of all women with ASC-US smears who underwent oncogenic HPV testing between July 2002 (when reflex testing with Hybrid Capture II was initiated at our site) and July 2003. To be eligible for inclusion, HPV DNA results had to be available. Data extracted from charts included demographic information as well as certain patient characteristics historically associated with HPV acquisition (e.g., number of sexual partners, age at first coitus).

**Results:** Of the 253 eligible women, 177 (70%) tested positive for oncogenic HPV subtypes at the time of an ASC-US smear. As compared to women who tested negative, this population was significantly younger (25.3 years versus 28.4 years, p=.01) and less likely to be married (13% versus 26%, p=.03). No significant differences between the two groups emerged with respect to smoking history, mean age at first intercourse, mean number of lifetime sexual partners, history of sexually transmitted infections or prior history of abnormal cervical cytology or treatment for neoplasia. A trend was seen in a protective effect of oral contraceptives among oncogenic HPV-positive women (13% versus 21%, p=.10). When stratified by age, 86% of the women under the age of 20 were positive for high-risk subtypes, compared to 53% of women over the age of 25 (p<.01). The protective effect of oral contraceptives was most pronounced among adolescent women and did not persist in women over the age of 25.

**Conclusion:** Given that the rate of oncogenic HPV positivity exceeded 85% in our population of adolescent women with ASC-US, the usefulness of HPV testing in this age group requires further validation.
Allison C. Strnad, MD

Human papillomavirus testing to predict residual cervical intraepithelial neoplasia following treatment.
A.C. Strnad, MD; L.A. Boardman, MD, ScM; M.M. Steinhoff, MD; S. Weitzen, PhD.

Objective: To assess the role of margin status, post-conization oncogenic HPV testing and post-conization cytology in predicting patients with residual neoplasia following treatment for cervical intraepithelial neoplasia.

Methods: Fifty-four women undergoing cervical conization at the Women’s Primary Care Center participated in this prospective trial. Women between the ages of 13 and 50 were eligible for inclusion if they met the following criteria: 1) CIN 2 or worse; 2) persistent CIN 1; or 3) cytologic-histologic discrepancy. At conization and first follow-up visit, oncogenic HPV testing using Hybrid Capture II was obtained. Routine follow-up consisting of cytology and colposcopy as indicated was performed every 4-6 months for one year. Residual disease was defined as CIN 1 or worse at any time during follow-up, or HSIL without a confirmatory biopsy.

Results: At the time of conization, 84% (41/49) tested positive for oncogenic HPV, while at the first follow-up visit, 36% (19/48) tested positive. Of the 54 women enrolled, 49 (91%) completed one follow-up visit, and 41 (76%) completed two or more visits. Of the three predictive variables considered, positive cone biopsy margins and abnormal cytology at follow-up were more sensitive in predicting residual disease as compared to positive oncogenic HPV test at follow-up (67% and 63%, respectively, versus 50%). Abnormal cervical cytology was marginally more specific (73% versus 67% for positive margin status at conization and 62% for positive HPV test).

Conclusion: With respect to residual disease, the presence of positive margins and abnormal cervical cytology following conization were more sensitive than oncogenic HPV infection at follow-up.

Presenting Fellows

Eric R. Sokol, MD

Results of urine cytology and cystoscopy in women with irritative voiding symptoms.
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Objective: To assess rates of urinary cytology abnormalities and cystoscopic outcomes in women presenting to a urogynecology clinic with irritative voiding symptoms.

Methods: All urinary cytologies sent between 01/01/2000 and 07/31/2003 for the evaluation of irritative voiding symptoms were reviewed. Data were then extracted from the charts of a subset of these patients to evaluate cystoscopic outcomes. Demographics, risk factors for urothelial cancer, laboratory results, and radiology imaging results were then analyzed and compared between patients with and without abnormal cytology and cystoscopy results.

Results: 1783 total urinary cytologies were reviewed; of these, 1661 were read as normal (93.2%), 112 (6.3%) were atypical, and 3 (0.2%) were unsatisfactory. Seven cytologies were categorized as suspicious or malignant, accounting for only 0.4% of all cytologies sent. Of the 564 consecutive women chosen for sub-analysis, cytology was normal in 91.5% and atypical in 8.5% of cases. No cytologies were suspicious or malignant. Cystoscopic findings were normal in 548 patients (97.2%). Only one patient (0.2%) was diagnosed with transitional cell carcinoma.

Conclusion: Urinary cytology and cystoscopy are low-yield tests and should not be routinely used in the initial evaluation of women with irritative voiding symptoms.
Tamara C. Takoudes, MD

Steroid effects on thrombopoietin in preterm preeclampsia preceptors.

T.C. Takoudes, MD; G. Messerlian, PhD; S. Weitzen, PhD; M. Malee, MD, PhD.

Objective: The objectives of this study are 1) to evaluate the effects of steroids on thrombopoietin (TPO), a cytokine produced mainly in the human liver that regulates platelet (PLT) production in patients with preterm preeclampsia (PEC) as compared to non-steroid treated term PEC and non-PEC controls and 2) to correlate TPO in cord blood specimens in normal pregnancy, term PEC and preterm PEC treated with steroids. Our hypothesis is that TPO and PLT will be inversely related and steroids will increase TPO in preterm PEC in comparison to pre-treatment levels. In addition, TPO will be higher in PEC than normal pregnancy when controlling for gestational age. Finally, TPO will be higher in fetal cord blood than maternal serum for all groups.

Study Design: Three groups of patients and cord bloods were examined: uncomplicated pregnant patients at 28-34 weeks and at delivery (group 1), patients with PEC>34 weeks (group 2), and patients with PEC less than 34 weeks who received a complete course of steroids (dexamethasone or betamethasone) for fetal benefit (group 3). PLT were measured by automated counter (Sysmex Corporation, SE 9000) and TPO was measured by a commercially available ELISA assay. Power analysis performed estimating a 2-fold increase in TPO for PEC compared to uncomplicated pregnancy to provide 80% power with a 5% level of significance showed 18 patients were needed in groups 1 and 2. PEC was defined by standard definitions from ACOG. Any subjects with underlying thrombocytopenia, chronic hypertension, autoimmune disease, multiple gestation, diabetes, premature rupture of the membranes, preterm labor and exposure to aspirin, indomethacin, smoking, alcohol or psychotropics were excluded from the study.

Results: There were 45 patients in the study (group 1, n=18; group 2, n=17; group 3, n=10). The mean gestational ages at delivery were group 1=39 weeks, group 2=37 weeks, and group 3=32 weeks. The mean maternal ages were group 1=32 years old, group 2=27 years old and group 3=28 years old. The mean birth weights were group 1=3440g, group 2=2616g, and group 3=1563g. Gestational age did not appear to affect TPO. The mean TPO levels were lowest in group 1 (112pg/mL) and highest in groups 2 and 3 (173pg/mL and 155pg/mL). Mean TPO levels decreased after 58 hours from first dose of steroids in preterm PEC, as compared to pre-steroids (155pg/mL prior and 128pg/mL post-steroids). Mean TPO values were higher in cord blood samples compared to maternal serum and highest in PEC (group 2=391pg/mL and group 3=396pg/mL) over non-PEC patients (group 1=349pg/mL).

Conclusion: Maternal TPO levels were increased in PEC over non-PEC patients. TPO decreases after steroids in preterm-PEC. Cord blood levels of TPO were increased over maternal levels and there was a trend for increased TPO levels in PEC cord blood over non-PEC patients. There did not seem to be an inverse relationship between TPO and PLT levels although small numbers may limit this study. PEC and steroids affect TPO levels.

Trevor Tejada-Berges, MD

Evaluating the efficacy of therapeutic vaccination with tumor-derived gp96 peptide complexes using a syngeneic rat model of ovarian cancer.

T. Tejada-Berges, MD; R. Binder, MD; P. Srivastava, MD; G. Rose, MD; W. Gajewski, MD; C. Granai, MD; M. Chung, MD.

Objective: Tumor-derived heat shock protein preparations, gp96 in particular, have been identified as endogenous immuno-therapeutic adjuvants. The goal of this study was to evaluate the efficacy of tumor-derived gp96 peptide complexes as immunotherapy against minimal residual ovarian cancer in an immunocompetent syngeneic rat model of ovarian cancer.
Methods: Forty-two Fisher® 344 rats were injected at time 0 with the rat ovarian cancer cell line, NuTu19, (10^6 cells ip/animal). The animals were then divided among three groups. Group 1 (n=14) was vaccinated twice weekly with 1 µg of tumor-derived gp96 peptide complexes intradermally. Group 2 (n=14) received 1 µg of normal liver-derived gp96, and Group 3 (n=14) was injected with 100 µg of sterile PBS. Prior necropsy studies using this experimental model had failed to demonstrate any gross disease at this time. Beginning on week 3, two animals in each group were sacrificed on a weekly basis and necropsies were performed to evaluate for tumor growth. Outcome measures were time to tumor development and tumor burden. Tumor burden was classified as: NED Ñ no disease; Stage 1 Ñ minimal peritoneal disease; Stage 2 Ñ moderate peritoneal disease without ascites; Stage 3 Ñ carcinomatosis with hemorrhagic ascites.

Results: All rats (100%) in the control group 3 developed evidence of disease, beginning on week 3. By week 5-6, they developed diffuse Stage 2-3 disease. All of the animals in this group died or were euthanized by week 7. In contrast, only 3 animals (21%) in the experimental group 1 developed gross evidence of disease. One developed Stage 2 disease on week 6 and another had Stage 3 disease by week 7. A third died on week 8. Eleven of fourteen animals (79%) remained disease-free following therapeutic vaccination. This included three animals that had survived through weeks 8 and 9. Seven animals (50%) in group 2 developed gross evidence of disease, ranging from Stage 1 to Stage 3. One animal died by week 8.

Conclusion: Vaccination with tumor derived gp96 peptide complexes effectively delayed the incidence of tumor development in this rat model of ovarian cancer and, in a large proportion of animals, completely eradicated all signs of disease. These observations suggest that the immune response elicited by tumor-derived gp96 appears to be sufficient to reject ovarian cancer cells, and warrants investigation in humans.