Objective: Our primary objective was to compare the difference in number of cervical excisional procedures in women <25 years with high grade cytology or histology who were managed expectantly versus those who underwent immediate excision. We hypothesized that women <25 years with high-grade cytology (HSIL, ASC-H, LSIL-H, AIS and AGC) or histology (CIN2 or greater) managed expectantly would have fewer excisions over the study period. Secondary objectives were 1) to compare the number of women, managed expectantly versus managed with immediate excision with CIN2+ two years after initial diagnosis and 2) to determine the rates of regression, progression and persistence among young women with high-grade histology.

Methods: This was a retrospective cohort study of all women < 25 years who presented to the WPCC with high-grade cytology or histology between 1999 and 2012. Women were grouped by management category (expectant versus immediate excision).

Results: Between 1999-2012, 493 women meeting eligibility criteria were seen at the WPCC, 417 are included in the primary analysis: 145 in the immediate excision group and 272 in the expectant management group. Throughout the study period, women in the expectant management group underwent a mean of 0.2 excisional procedures compared to a mean of 1.1 excisional procedures in the immediate excision group (p = <0.0001). 22% of the women in the expectant group eventually underwent an excisional procedure. Two years after initial presentation, 27.4% of women in the expectant group and 3.5% of women in the immediate excision group had CIN2+ on biopsy. Of the 129 women with CIN2+ on initial biopsy who were expectantly managed, 79 (61.2%) showed regression, and only 10 (7.8%) showed progression from CIN2 to CIN3. All regressions took place by year 5, with the majority (72/79, 91%) by year 2. There were no cancer diagnoses at baseline or at end of study period.

Conclusion: In young women with high-grade dysplasia managed expectantly, 61% showed regression. If all women in this study had been expectantly managed, 88 excisions may have been avoided. No cases of cancer were identified, further supporting the safety of expectant management for young women with high-grade cervical lesions.
**Title:** Obesity Risk Awareness in Endometrial Cancer Survivors  

**Authors:** Elizabeth V Connor MD, Chris Raker SCD, Ashley R Stuckey MD  

**Objective:** In women with endometrial cancer, obesity is associated with poorer quality of life and higher all-cause mortality. Our objective was to assess whether endometrial cancer survivors were able to accurately classify their weight and identify the association between obesity and risk of endometrial, breast, and colon cancers.  

**Methods:** This was an IRB-approved, survey-based study of women ages 18-80 with a diagnosis of endometrial cancer. Patients were excluded if they were less than 6 months from hysterectomy or less than three months from chemotherapy or radiation. Patients meeting criteria were given a survey at their follow-up appointment, and returned the 24 question survey at the end of their visit. Statistical analysis was completed using Fisher’s exact test, T-test, ANOVA, Wilcoxon rank-sum test, or Kruskal-Wallis test. P-values were two-tailed with p<0.05 considered statistically significant. A sample size of 110 surveys would be powered to detect a 10% difference in perceived weight and a 30% difference in awareness of cancer risk.  

**Results:** 140 women met inclusion criteria and were provided surveys. 133 surveys (95.0%) were completed. Mean age was 63.2 years (range 35-80) and mean BMI 33.4 (17.6-72.2). Patients were primarily Caucasian (88.7%) and a majority (67.8%) reported education beyond the high school level. Of obese women with BMI 30-35, 12.9% identified themselves as obese, compared with 32.0% of severely obese women (BMI 35-40), and 72.7% of morbidly obese women (BMI > 40). Ability of the patient to correctly classify their weight correlated significantly with increasing education level (p= 0.02). 77% of all patients had discussed weight with their primary care doctor, while only 38% had discussed weight with their oncologist (p<0.0001). The majority were unable to identify obesity as a risk factor for breast (49.6%), colon (48.1%), and endometrial cancer (44.4%).  

**Conclusion:** Women with endometrial cancer had difficulty accurately classifying their weight, especially if they were obese to severely obese (BMI 30-40). Given the inconsistency between patient weight and perception of cancer risk, this represents an opportunity for gynecologic oncologists to educate their patients about weight control and its correlation with improved overall survival and quality of life.
Title: The effect of neoadjuvant depot medroxyprogesterone acetate on glandular cellularity in women with complex atypical hyperplasia or grade 1-2 endometrioid adenocarcinoma awaiting hysterectomy

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Preceptor: Katina Robison, MD
Other authors: Melissa DaCosta, PharmD; Valery Danilack, PhD; Elizabeth Kalife, MD; Chris Raker, PhD; Jennifer Sawicky, PharmD; Kamaljeet Singh, MD

Objective: To determine whether injection with depot medroxyprogesterone acetate [DMPA] decreases glandular cellularity in hysterectomy specimens among women with complex atypical hyperplasia or grade 1-2 endometrioid adenocarcinoma as compared to women injected with placebo solution.

Methods: This is a randomized, double-blind, placebo-controlled study. A total of 76 women will be recruited during outpatient visits at the Program in Women’s Oncology, and recruitment is ongoing. Exclusion criteria include medical contraindications to DMPA, non-English language, and recent treatment with progestins. Outcomes include change in glandular cellularity as defined in GOG 211, quality of life as determined by the Functional Assessment of Cancer Treatment Endometrial Cancer [FACT-En] survey, and clinical outcomes such as need for transfusion, and further pathologic, histologic and immunohistochemical markers. The study is powered to detect a 20% decrease in glandular cellularity between biopsy specimen and hysterectomy specimen among women treated with DMPA as compared to women who received placebo injection.

Results: At the time of abstract deadline, 8 patients have been recruited over a 1-month recruitment period. All 4 eligible patients who declined to participate did so because they did not want to participate in research. Both patients who have undergone surgery to date have satisfactorily completed and returned the FACT-En survey. Further recruitment is ongoing.

Conclusions: Based on extensive experience described in the medical literature, it is reasonable to infer that treating women who have a diagnosis of complex atypical hyperplasia or grade 1-2 endometrioid adenocarcinoma preoperatively with DMPA might be both a meaningful temporizing measure for their cancer and confer symptomatic relief of abnormal uterine bleeding. The findings of this study may have particularly important implications for women who can expect a long wait time to surgery.
**Title:** A NOVEL 3-DIMENSIONAL (3D) CELL CULTURE FOR THE STUDY OF TROPHOBLAST DIFFERENTIATION, BEHAVIOR, AND INVASION

**Authors:** Valerie A Flores, MD, Lori Underhill, PhD, Paula M Krueger, BS and Jared C Robins, MD Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, 90 Plain St Providence, RI, United States, 02905.

**Objective:** The hallmark of early trophoblast differentiation is the formation of a spherical structure with close cell-cell contact. Yet most of the information regarding trophoblast gene expression has been derived from cells in a monolayer. We hypothesize that the behavior of trophoblast cells cultured in 3D spheres will be dramatically different when compared to a traditional monolayer culture.

**Methods:** Immortalized trophoblast cells (TCL-1) were cultured to 70% confluence in monolayers or to spheroids in a non-adhering micromold bioreactor as previously described. RNA was extracted and hybridized to Affymetrix Human Gene 1.0 ST microarray. Affymetrix Expression Console (v 1.1) was used to normalize data and determine signal intensity. Real-time quantitative PCR was performed on genes of interest. Western blot (WB) analysis was performed on cellular membrane preps to detect sodium/potassium (Na/K) pumps.

**Results:** Microarray of TCL-1 monolayer and spheroid cell cultures demonstrated that 58 genes were differentially expressed. Pathway analysis revealed that the most common genes were those involved in cellular invasion including: MMP10, adrenomedullin (ADM) and angiopoietin-like 4(ANGPTL4). WB demonstrated induction of Na-K pumps in spheroids, but not in monolayers.

**Conclusions:** We previously reported that trophoblast cells cultured in a 3D system form trophoblastic vesicles (Robins et al, 2010). Here we demonstrate that these cells have a dramatically different transcriptome when compared to cells in monolayer; invasive gene expression is highly induced. Gene expression associated with the induction of neovascularization, including ADM and ANGPTL4, are induced in the 3D culture. Na-K pump activity, the hallmark of blastulation, provides further support for the complex functionality of spheroids. We conclude that 3D culture better recapitulated physiology and therefore should be used to study the behavior of trophoblast cells.
Evaluation of universal immunohistochemistry screening for diagnosing Lynch syndrome in endometrial cancer patients at a tertiary care center

Authors. Erin G. Hartnett
Preceptor: Ashley Stuckey, MD and Carolyn McCourt, MD

Objective. To compare genetic counseling referrals and rates of Lynch syndrome (LS) detection during the initial year of universal screening of endometrial cancers to those in the previous year when screenings and referrals were performed at physicians’ discretion based on family or personal history.

Methods. We performed a retrospective cohort study of all women who underwent a hysterectomy for endometrial cancer at Women and Infants Hospital between September 1, 2012 and August 31, 2014 (n=435). A universal screening protocol was initiated on September 1, 2013 and utilized immunohistochemistry (IHC) for MMR proteins MLH1, MSH2, MSH6 and PMS2. Cases with absent MLH1 staining were reflexed to MLH1 promoter methylation testing. The first cohort consisted of women who presented prior to initiation of the screening protocol and were selectively screened (n=235). In the second cohort, women presented after initiation of this protocol and were all screened for LS (n=205). Genetic counseling referrals in both cohorts were based on risk factors (family or personal history) and/or IHC results. Categorical variables were compared using chi-square test and Fisher’s exact test and continuous variables were compared using the t-test.

Results. Overall, a greater proportion of individuals in the universal screening cohort were referred to genetic counseling than in pre-screening cohort (7.3% vs. 2.2%, p<0.05). During the universal screening period, 43 patients (21%) had abnormal IHC results: 1 lacked expression of MSH6/PMS2, 5 lacked MSH6 and 37 lacked MLH1/PMS2. Of the 37 patients who lacked MLH1/PMS2 expression, 36 had MLH1 promoter methylation and were assumed to have sporadic cancers. The 7 patients with abnormal screens were referred to genetic counseling. None of these patients met traditional screening guidelines. Three women had positive germline testing confirming LS diagnosis.

Conclusions. The implementation of a universal screening protocol for LS utilizing IHC in endometrial cancer leads to higher rates of genetic counseling referral than referral based on family or personal history alone. All of the patients diagnosed with LS in our initial year of universal screening would have been missed by traditional criteria. Universal screening of endometrial cancers is critical for identifying women at high risk for LS.
Title: Is a massive transfusion protocol associated with improved maternal outcomes in obstetric hemorrhage?

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Objective: A massive transfusion protocol (MTP) is a structured system for delivery of blood products. MTP use has been shown to improve outcomes in a trauma population, but has not been studied in an obstetric setting. We sought to compare maternal morbidity outcomes before and after implementation of an MTP.

Methods: We performed a retrospective cohort study of massive obstetric hemorrhage between 2007 and 2014 at our tertiary care hospital. Massive obstetric hemorrhage was defined as hemorrhage in the peripartum period treated with 4 or more units of packed red blood cells (pRBCs). Patients with massive obstetric hemorrhage were compared before and after July 1, 2010, the date the protocol was put into practice. Our primary outcome was any indicator of severe maternal morbidity, which was defined as either unplanned peripartum hysterectomy, intensive care unit (ICU) admission, acute kidney injury (AKI), mechanical ventilation or documented coagulopathy. Data were obtained through chart abstraction and blood bank transfusion records and analyzed using Chi-square and Fisher’s exact test.

Results: There were 197 massive obstetric hemorrhages (83 pre-MTP implementation and 114 post-MTP implementation) during the study period. Pre-implementation of the massive transfusion protocol, 37.3% of women received fresh frozen plasma (FFP) compared to 60.5% post-implementation (p=0.001). Similarly, 21.7% of women received platelets pre-MTP versus 36.8% post-MTP (p=0.02). There were no maternal deaths in either group. AKI was significantly more likely in the pre-MTP period (15.7% vs. 3.5%, p=0.003). There was no difference in indicators of maternal morbidity in the pre and post-implementation groups.

Conclusion: Implementation of a massive transfusion protocol in those with massive obstetric hemorrhage was associated with increased administration of FFP and platelets, and a decreased incidence of acute kidney injury, but no difference in overall maternal morbidity.
Are serum and placental levels of enzymes involved in the production of endogenous carbon monoxide and bilirubin elevated in preeclampsia with severe features?

Warren J. Huber III, PhD MD, James Padbury MD, and Brenna Hughes, MD MSc

Preceptor: Brenna Hughes, MD MSc

**Objective:** To compare serum levels of Heme Oxygenase-1 (HO-1), Cytochrome P450 Reductase (CPR), and Biliverdin Reductase (BVR) among pregnant women with preeclampsia with severe features versus gestational age-matched controls. Characterizing the serum levels of these enzymes responsible for the production of the cellular protective molecule bilirubin and endogenous carbon monoxide (CO) in pregnancies complicated by preeclampsia with severe features compared to normal pregnancies will aid in understanding one of the initial mechanisms of cellular defense against hypoxic stress.

**Methods:** Prospective cohort study from June 2014 to November 2014 of women with preeclampsia with severe features between 24’0 to 41’6 weeks’ gestation and gestational age-matched controls. Blood samples were collected prior to delivery and serum levels of HO-1, CPR, and BVR were measured by ELISA sandwich assay. The primary outcome was tested by comparing median values of the serum enzyme levels between groups with Wilcoxon rank sum test

**Results:** 40 women were enrolled in the study and all serum samples were analyzed: 20 in the preeclampsia with severe features group and 20 in the control group. Baseline characteristics were similar between the two groups. All three enzymes of interest were elevated in the serum of patients with preeclampsia with severe features compared to controls. Serum HO-1 levels were 33.5 (interquartile range 4.1 – 16.3) vs 17.2 (interquartile range 1.3 – 5.6) mg/ml, P=0.02. BVR levels were 53.9 (interquartile range 28.0 – 83.1) vs 32.8 (interquartile range 18.9 – 38.8) mg/ml, P=0.03. CPR levels were 15.8 (interquartile range 1.9 – 23.7) vs 2.2 (interquartile range 0.9 – 2.1) mg/ml, P<0.001.

**Conclusions:** Serum levels of the cytoprotective enzyme system composed of HO-1, CPR, and BVR are elevated in women with preeclampsia with severe features. This suggests that these enzymes are involved in the cellular protective mechanisms that respond to the inflammatory cascade potentiated in preeclampsia with severe features.
Title:
Low prenatal care adherence increases the risk of NICU admission among women with diabetes mellitus

Authors:
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Preceptors: Lindsay Maggio, MD; Donald R. Coustan, MD
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Objective:
To determine the impact of poor prenatal care adherence in women with preexisting diabetes mellitus (DM) on the rate of NICU admission, adverse maternal/neonatal outcomes, and glycemic control.

Methods:
Retrospective cohort study of women with preexisting DM in a Diabetes in Pregnancy program who delivered between 2006 and 2014 (N=443). Adherence with prenatal care was a ratio of appointments attended to appointments scheduled. The primary outcome was the rate of NICU admission. Secondary outcomes included adverse maternal and neonatal outcomes and glycemic control.

Results:
Prenatal care adherence compared the 1st quartile to the 2nd-4th quartiles. First quartile subjects were more often publically insured (75.8% vs. 65%; p=0.03), had a history of self-reported tobacco (32.5 vs. 14.9%; p<0.001), alcohol (4.2% vs. 0.3%; p=0.006), or drug use (16.7% vs. 3.7%; p<0.001), and prior psychiatric history (55 vs. 35%; p<=0.001). They demonstrated less adherence with glycemic monitoring (49% vs. 68%; p<=0.001), more fasting and post-prandial glucose values above target (54 vs. 45%; p<0.001; 47% vs. 42; p=0.005), earlier GA at delivery (36.5 vs. 37.5 weeks; p<0.001), lower birth weight (3118 vs. 3460 grams; p<0.001), and were less likely to have a last A1C less than 7 (43.1 vs. 67.1%; p<0.002).

Patients in the lowest quartile of prenatal care adherence were more likely to have their neonates admitted to the NICU (54.6 vs. 38.1; p=0.002) and the length of stay there was longer (15.6 vs.13.5 days; p=0.03). Multiple logistic regression showed that insurance carrier, psychiatric history, and stated drug, tobacco or alcohol use, attenuated the difference in NICU admission rates seen (aOR 0.65 (0.41, 1.01; p=0.055), and might be potential modifiable risk factors for poor adherence.

Conclusion:
Pregnant women with preexisting DM with poor prenatal care adherence are more likely to have their neonates admitted to the NICU, and have worse glycemic control. Socioeconomic risk factors appear to contribute to suboptimal adherence.