Title: Cisplatin and radiation induce loss of ovarian reserve by activation of TAp63 through different mechanism

Summary: Previously, imatinib, an ABL kinase inhibitor, was shown to protect primordial follicles against cisplatin. Accordingly, the phosphorylation of TAp63 by c-Abl/ABL1 has been implicated as the key pathway of chemotherapy-induced oocyte death. We have demonstrated that oocytes specific conditional knockout (cKO) mice for Trp63 gene, encoding TAp63, were insensitive to cisplatin-induced follicle loss, supporting the essential role of TAp63 in cisplatin-induced oocyte apoptosis. On the other hand, involvement of c-Abl in oocyte apoptosis was indirectly supported by inhibitor studies: Two Abl kinase inhibitors with different modes of action, imatinib and GNF-2, protected primordial follicles from cisplatin.

Objective: To explore the function and requirement of c-Abl in the TAp63-regulated apoptosis of premature oocytes.

Sample: We generated transgenic mice that have oocyte specific conditional knockout of abl1 gene from the primordial oocytes, using GDF9-iCre. These mouse ovaries were compared with those of oocyte specific conditional knockout of Trp63.

Methods: Ovaries were cultured and tested in vitro with cisplatin and radiation. The number of primordial follicles was quantitatively counted and the survived oocytes were stained with oocyte specific markers. Furthermore, Chk2 inhibitor was tested in ovarian culture system with cisplatin.

Results: Primordial follicles of oocyte specific Abl1 cKO mice underwent apoptosis in response to cisplatin, indicating that oocytic c-Abl is dispensable for the cisplatin-induced oocyte death. Moreover, hyperphosphorylation of TAp63 was induced by radiation in the absence c-Abl, indicating that the previously proposed role of c-Abl in phosphorylation of TAp63 was incorrect. The presence and absence of TAp63 hyperphosphorylation in the apoptosis of oocytes induced by radiation and cisplatin, respectively, strongly suggested that these two anti-cancer treatments activated TAp63 through different molecular mechanisms. Indeed, imatinib and GNF-2, which effectively protected oocytes from cisplatin, did not inhibit radiation-induced apoptosis and TAp63 hyperphosphorylation in oocytes. In contrast, the radiation-induced oocyte death and TAp63 phosphorylation were effectively blocked by a CHK2 inhibitor, Chk2 Inhibitor II hydrate, suggesting that radiation activates TAp63 via phosphorylation by CHK2. Interestingly, although cisplatin did not induce hyperphosphorylation of TAp63, the CHK2 inhibitor II hydrate still protected primordial follicles from cisplatin, suggesting that kinases activity that are inhibited by Chk2 Inhibitor II hydrate is essential for cisplatin-induced apoptosis in primordial oocytes.

Conclusions: This current study has highlighted that Chk2 Inhibitor II hydrate treatment might be a promising treatment for the prevention of ovarian reserve loss in women undergoing anti-cancer therapy because Chk2 Inhibitor II hydrate effectively protects oocyte against cisplatin as well as radiation.
Engineering a three-dimensional human ectocervical tissue model to study hormonal regulation and immune response of the female reproductive tract. Kelly McKinnon¹, Paul Hoover², Teresa Woodruff¹, Spiro Getsios², Department of Obstetrics and Gynecology¹, Department of Dermatology², Northwestern University Feinberg School of Medicine, Chicago, IL.

The ectocervix plays a major role in childbirth, infectious disease transmission, and contraception. It has a stratified squamous epithelium that is composed of multiple differentiated cell layers. The basal layer contains progenitor cells that produce the parabasal, intermediate and superficial layers. This epithelium undergoes constant regeneration throughout life and is modified during the menstrual cycle in response to ovarian hormones. In addition to the morphological changes that occur throughout the menstrual cycle, the innate immune system of the female reproductive tract (FRT), including the ectocervix, is directly and indirectly regulated by ovarian hormones. Though much is known about hormonal regulation of other tissues in the FRT, the ectocervix remains vastly understudied. Mouse models and 2D cultures have traditionally been used to study reproductive biology; however, mouse models do not accurately represent human FRT anatomy or physiology, and more importantly are not natural hosts to pathogens that can infect humans, whilst 2D human cell cultures do not accurately reflect the stratified architecture of a differentiated ectocervix. Therefore, using primary epithelial cell cultures initiated from human ectocervix, we have engineered a 3D model of this stratified epithelium that recapitulates aspects of the *in vivo* human physiology. Primary ectocervix epithelial cells were grown on a collagen-based stromal scaffold at an air-liquid interface, and formed multiple differentiated layers, as shown by histology and cytokeratin profiles. Cytokeratin-14 was found in the basal layer, and cytokeratin-13 in the more intermediate and superficial layers. Additional differentiation markers typical of native ectocervix, such as p63 and MUC4 were also present in these 3D tissue cultures. This model will be a critical tool for understanding fundamental mechanisms of the ectocervix involved in homeostasis as well as diseased states of the ectocervix, such as host-pathogen interactions and oncogenic transformation. Supported by UH3TR001207 (NCATS, NICHD, NIEHS, OWHR, NIH Common Fund).
Title: Microfluidic platform supports mouse ovarian follicle development and recapitulates human 28 days menstrual cycle

Summary: The main female reproductive organs include ovary, fallopian tubes, uterus, cervix, and vagina. These organs function in relation to each other to provide hormonal support and the anatomical structure through which gametes travel for the embryo to undergo development, transport, implantation and placentation.

Objective: Our objective is to mimic human 28 days menstrual cycle in vitro by culturing mouse ovarian follicles in the microfluidic platform, and develop an ex vivo female reproductive tract that can be used for reproductive toxicology and therapeutic discovery based on the ovarian hormone production and their effects on the downstream gynecologic tissues.

Sample: Mouse primary follicles were isolated from day 12 CD-1 mice and multiply encapsulated in 0.5% alginate hydrogels and cultured in the microfluidic platform.

Method: To mimic human 28 days menstrual cycle, follicles were cultured for 14 days with follicle-stimulating hormone (FSH) to phenocopy the follicular phase, which was followed by human chorionic gonadotropin (hCG) administration on day 14 to trigger the luteal phase and an additional 14 days of culture without FSH.

Results: Results indicated that encapsulated in vitro follicle growth (eIVFG) was supported from primary to antral stage in the microfluidic system. After hCG treatment, follicles produced mature metaphase II oocytes with barrel-shaped bipolar spindles and tightly aligned chromosomes. During the follicular phase, estradiol production increased and peaked on day 14 when follicles reached maturity. During the luteal phase, the progesterone levels increased significantly and peaked 2 days after the hCG treatment; and, the histologic analysis indicated that follicles initiated luteinization at the cellular level based upon granulosa cell hypertrophy.

Conclusions: Taken together, our results demonstrate that the microfluidic platform provides a dynamic environment in which hormone production is maintained over a 28 day in vitro hormone cycle. This tool provides great potential to monitor rapid ovarian hormone changes and their effect on downstream reproductive tissues in vitro, and to provide a model to study the reproductive toxicology and therapeutic discovery.
Presenting Author: Caroline F. Healy BS  
Position: Clinical Research Coordinator  
Principal Investigator: Seema A Khan MD  
Department: Pathology/Breast Surgery  
Clinical, or Basic Science, or Public Health and Social Sciences: Basic Science  

Email: chealy1@nm.org

Title: Case-Control study of hormone receptor expression in benign breast and cancer risk.

Summary/Objective: Previous studies have shown that hormone receptor expression in non-proliferative epithelium (NPE) indicates increased breast cancer risk, whereas other studies have been null. We assessed estrogen and progesterone receptor (ER, PR) and Ki67 expression in NPE of newly diagnosed breast cancer cases and benign disease controls using contemporary immunohistochemical (IHC) methods and digital image analysis.

Sample/Methods: Formalin-fixed paraffin-embedded breast samples were collected from women treated between 1994-99; (171 cases and 169 controls, age-matched); 4-µm sections were stained for ER (ThermoScientific/SP1, 1:200-pH6), PR (Dako/M3569, 1:1600-pH6) and Ki67 (Dako/MIB-1, 1:100-pH6) on Leica Bond Max and Dako automated stainers. The NPE portions of the digitized slides were sampled in random fashion and evaluated blindly with Aperio Spectrum software; % positive cells were scored for ER and PR, and Ki67, and categorized into quartiles. Wilcoxon rank-sum test and logistic regression with age adjustment were used for pairwise comparison. Spearman’s rank correlation test and one-way ANOVA test with Sidak adjustment were used for the correlation and comparison among multiple markers.

Results: The mean age was 49 years for cases and 48 years for controls. Overall, there was no significant difference between the cases and controls for ER, PR or Ki67 expression. In analyses stratified by menopausal (M) status, post-M ER % positivity was significantly higher in cases than controls (34.0 vs 29.8, OR=1.487, p=0.007). ER was significantly higher in post- than in pre-M cases (p<0.0001). ER and PR were positively correlated among cases (R=0.433, p<0.0001) and controls (R=0.547, p<0.0001). Ki67 was significantly lower in post- than in pre-M controls (p=0.004).

Conclusion: ER expression in benign non-proliferative breast epithelium is significantly higher in postmenopausal cases and increased ER expression may indicate increased breast cancer risk in these older women.
The zinc spark is a non-invasive marker of mammalian egg and embryo quality

**Summary:** Activation or fertilization of mammalian eggs initiates a series of extracellular “zinc (Zn) sparks” that are necessary to induce the egg-to-embryo transition. However, despite the prominence of this Zn-efflux event, it is unknown if the Zn sparks have any effects on the embryonic developmental outcomes. To test the hypothesis that profiles of Zn sparks are correlated with embryo development and can be used as a biomarker of embryo quality, we monitored Zn sparks in individual mouse eggs following *in vitro* fertilization (IVF) or parthenogenetic activation (Ionomycin) and tracked the development of the resulting zygotes and parthenotes. In this study we found a significant correlation between the profiles of Zn sparks and embryo development in mouse. We also did the first-time investigation to show that the Zn spark mechanism is conserved in human eggs suggesting the significant biological relevance and clinical applicability of Zn sparks.

**Objective:** To test if the zinc spark is a non-invasive marker of mammalian egg and embryo quality.

**Sample:** Mouse and human MII eggs

**Methods:** We monitored Zn sparks in individual mouse eggs following *in vitro* fertilization (IVF) or parthenogenetic activation (Ionomycin) and tracked the development of the resulting zygotes and parthenotes. In this manner, we were able to directly determine how the Zn spark profile correlated with three developmental outcomes: 1) unactivated eggs, 2) activated eggs that did not reach the blastocyst stage (non-blastocyst), and 3) activated eggs that reached the blastocyst stage (blastocyst). To further understand whether Zn sparks reflected blastocyst quality, we examined how the Zn spark profile related to blastocyst cell number. We also conducted preclinical studies in human eggs to validate the potential clinical value of the Zn spark technology.

**Results:** A significantly higher amplitude and larger total Zn release compared to the profiles of non-blastocysts characterized the Zn spark profiles of blastocysts (p<0.01 and p<0.05 respectively for IVF, p<0.01 and p<0.001 respectively for Ionomycin). Unactivated eggs either had no Zn sparks or had the lowest Zn release profiles compared to those eggs that initiated preimplantation embryonic development. Interestingly, we also found that the blastocysts with more cells were characterized by higher Zn spark amplitude than the blastocysts with fewer cells (p<0.0001). We found that reducing intracellular Zn using a Zn-specific chelator (TPEN) was sufficient to initiate human egg activation suggesting a biological function for zinc flux in early human development. Moreover, Ionomycin-induced parthenogenetic egg activation resulted in a Zn spark that was tightly coordinated with a rise in intracellular calcium. We also observed variability in the Zn spark profile among human eggs, both between and among individuals, suggesting potential underlying differences in gamete quality.

**Conclusion:** In summary, the data in this study suggest that the Zn spark is highly conserved and is a robust non-invasive marker of egg quality with significant biological relevance and clinical applicability.
Title: Sex Bias Exists in Basic and Translational Surgical Research

OBJECTIVE: While the Revitalization Act was passed in 1993 to increase enrollment of women in clinical trials, there has been no significant focus on sex disparity in basic and translational research. We hypothesize that sex bias exists in this surgical arena.

METHODS: All manuscripts in Annals of Surgery, American Journal of Surgery, JAMA Surgery, Journal of Surgical Research, and Surgery in 2011-2012 were reviewed. Data abstracted included study model, sex, location, and specifics regarding sex-based reporting. Data were analyzed using SPSS.

RESULTS: Of 2,347 articles reviewed, 618 included animals and/or cells. For animal research, 22% of the publications did not specify sex. Of the papers that did specify sex, 62% of publications included only males, 13% only females, 2% both sexes. A greater disparity existed in the number of animals studied: 16,152 (84%) males and 3,173 (16%) females (p<0.0001). For cell research, 76% of the publications did not specify sex. Of the papers that did specify sex, 17% of publications included only males, 5% only females, 2% both sexes. Only 7 (1%) studies reported sex-based results. For publications on female-prevalent diseases, only 6% studied female animals, while 62% did not state the sex. More international publications studied only males (67% vs. 38%, p<0.0001) whereas more national publications did not specify the sex (47% vs. 20%, p<0.0001). Sub-analysis of a single journal showed that across three decades, male-only studies and usage of male subjects became more disparate.

CONCLUSIONS: Sex bias exists in basic and translational surgical research. Since biomedical research serves as the foundation for subsequent clinical research and medical decision making, it is imperative that this disparity be addressed. Scientific journals should require authors to document sex and justify single-sex studies.
Title: Metarrestin: A Novel Compound Active Against Ovarian Cancer

Summary
A novel drug metarrestin (ML 246) was identified through a screen of compounds that disrupted the perinucleolar compartment (PNC), which is a nuclear structure associated with the metastatic potential of cancer cells. In vivo analyses of various solid tumors show a significant inhibition of distant metastases and reduction in metastatic tumor volume when treated with metarrestin.

Objective
In this study, the effect of ML246 on ovarian cancer cells was tested in vitro and in vivo.

Methods
The PNC prevalence (the percentage of cells containing at least one PNC) in SKOV3 and OVCAR3 ovarian cancer cell lines treated with two doses of metarrestin was determined by immunofluorescence with SH54, a monoclonal antibody that specifically recognizes PTB, an RNA binding protein that is highly concentrated in the PNC. A cell viability WST assay and a Matrigel invasion assay using a transwell system were performed. A mouse model using SKOV3 transfected with Luciferase was developed by surgically placing collagen cell pellets under the bursa of one ovary in nude mice, and subsequently treated with metarrestin 25 mg/kg by intraperitoneal injection for 7 weeks on a weekday schedule using cisplatin and vehicle as controls. Mice were sacrificed 10 weeks after xenografting.

Results
SKOV3 and OVCAR3 cells are high in PNC prevalence. When treated with metarrestin, the PNC prevalence and the number of cells that contain multiple PNCs were significantly reduced. Cell viability assay showed minimal cell toxicity, in which treatment up to 20 uM metarrestin did not induce growth inhibition. Significant decreased cell viability was only observed when treated with metarrestin at 50 uM. Metarrestin significantly inhibited invasion of SKOV3 and OVCAR3 cells. Mice with SKOV3 tumors treated with metarrestin appear to have fewer macro-metastatic lesions on the intestines and subcutaneous tissues and none on the kidneys or diaphragm when compared to those in the cisplatin and vehicle groups. Primary tumor size, however, was not decreased by metarrestin. Mouse body weight remained stable and no significant toxicities were noted.

Conclusions
Metarrestin effectively reduces PNC prevalence in ovarian cancer cell lines, and significantly attenuates invasion of ovarian cancer cells without significant growth inhibition. Preliminary data suggests an attenuation of metastasis in mice who received metarrestin with minimal toxicity. We are currently testing metarrestin on patient derived xenograft lines in mice.
Title: From a whole animal to the single cell: Identifying transmission sites and characterizing HIV target cells in the female reproductive tract (FRT).

Summary: Using the two reporter virus vector that undergoes a single round of replication we are able to monitor which parts of the FRT are susceptible to the virus penetration and what is the nature of the first cells infected. Our findings demonstrate that the entire FRT including the ovaries and local draining lymph nodes are readily infected and that majority of the initially targeted cells are CD4 positive T cells.

Objective: The main focus of this work is to determine which areas of FRT are targeted by HIV during male-to-female transmission of the virus and to phenotype the first infected cells.

Methods: In order to address these questions our lab developed a novel method for detecting HIV in the FRT after vaginal infection. We use the animal model in which the female rhesus macaques are vaginally challenged with SIV pseudoviral vector with JR-FL R5 HIV envelope capable of undergoing the single round of replication. This vector express two different reporters so that we could detect where the virus goes within the FRT, and what specific cell types it targets. The first reporter, called luciferase, causes the virus to emit a yellowish glow and can be detected in intact FRT harvested from the monkeys using a special in vivo imaging system (IVIS). The second reporter, called mCherry, emits red fluorescence that can be detected using a confocal microscope and allow us to pick out individual infected cells and to phenotype them using variety of cell surface markers.

Results: Using in vivo imaging system to detect luciferase, we detected virus in the vaginal tissue, labia, ecto- and endocervix, and even in the ovaries. Lymph nodes also showed signs of infection, although not as consistently. Focusing in on these areas, we were then able to look for mCherry fluorescence in tissue sections with a confocal microscope to identify individual cells that had been infected with the virus. Infected cells were validated by looking at the direct fluorescence of the mCherry protein and by staining with anti-luciferase antibody. The spectral imaging technique reviled that the infected cells had a single peak at 610nm wavelength when only direct mCherry fluorescence was monitored, while an additional peak at 680nm wavelength was observed when anti-luciferase antibody was used in conjunction with the Cy5 secondary antibody. Transduced cells identified to date include CD4 positive T cells, identified as mCherry and luciferase expressing cells staining positive for CD4 and CD3.

Conclusions: From these findings, we were able to conclude that HIV infects more regions of the FRT than previously believed and that it does not have a preference for discrete regions of the FRT, but rather infects indiscriminately. Our results strongly imply that we need to alter our current strategies for prevention of HIV infection via male-to-female transmission by focusing our energies on developing a vaccine or virus-killing agent that can be widely distributed across the FRT, as opposed to limiting the distribution to a certain area.
Presenting Author: Miles Fuller
Position: Student
Principal Investigator: Brian T. Layden M.D./Ph.D
Department: Endocrinology
Clinical, or Basic Science, or Public Health and Social Sciences: Women’s Health Research
Email: mfuller17@u.northwestern.edu

Title: Gut-derived Short Chain Fatty Acids contribute to Gestational Glucose Homeostasis via FFAR2 Signaling in Pancreatic Beta Cell

Summary: Throughout pregnancy, dynamic changes in maternal islet function occur to compensate for heightened insulin resistance, maintain metabolic stability in the mother and are linked to the programming of fetal energetics. Previously, we showed that Free Fatty Acid Receptor-2 (Ffar2) transcript expression was increased in mouse islets during the insulin resistant phase of pregnancy, implying a role of FFAR2 in islet adaption.

Objective: As short chain fatty acids (SCFAs), the ligands for FFAR2, are primarily derived from gut microbial fermentation, we hypothesized that SCFAs and the gut microbiome contribute to glucose homeostasis regulation during pregnancy through a novel interaction with FFAR2.

Methods: We bred female transgenic mice with FFAR2 genetically deleted in all tissues (Ffar2-/-) and compared measures of glucose homeostasis to wildtype littermates before, during and after pregnancy. A long-term term treatment with high-dose broad range antibiotics was implemented to modulate the mouse gut microbiome in order to elucidate its contribution to pancreatic beta cell-specific FFAR2 signaling.

Results: This study revealed impaired glucose tolerance in the Ffar2-/- mice during pregnancy. As insulin tolerance in the Ffar2-/- mice was not impaired, a deficiency in islet function during pregnancy was evaluated where we observed diminished ligand induced insulin secretion and impaired beta cell expansion and proliferation as compared to matched female WT littermates. Next, exploring SCFA levels in these mice, we observed that both serum and cecum-derived SCFAs were altered by pregnancy in a genotype-dependent manner. Likewise, the gut microbiota compositional diversity was also influenced by pregnancy and mouse genotype. Finally, we investigated the impact of antibiotic ablation of the gut microbiota and determined that antibiotic treatment induces specific changes to cecum and plasma SCFA levels, and consequently influences glucose tolerance prior and during pregnancy.

Conclusions: Together, these results suggest that a novel relationship may exist between beta cell specific-FFAR2, the SCFAs that activate this receptor, and the gut microbiota in regulating gestational glucose control.
Title: Preferential infection of Th17 cells by SIV in macaques during transmission

Summary: Initial infection events at mucosal sites eventually establish systemic viremia. Studying this process is complicated by the inability to find the small number of infectious events in whole organ systems. To identify the first targets of infection, we recently developed a dual luciferase/fluorescent reporter system that allows us to find foci of cells 2 days after transmission. We hypothesized that the reporter vector would behave in the same way as replicating virus and that we could use the reporter to find infection. We vaginally challenged rhesus macaques with our reporter and SIVmac239. Sites of infection are identified by luciferase expression. We now address the question of what phenotype of cells are infected.

Objective: Defining the initial cell types infected is critical to understanding HIV transmission, dissemination and pathogenesis.

Methods: Rhesus macaques are challenged with reporter virus and replicating SIV. 48 hours later, animals are sacrificed and their reproductive tracts removed. We detect foci of infection by luciferase expression by in vitro imaging system (IVIS). Single copies of integrated DNA are detected by nested PCR. We are able to phenotype the T cell subsets infected based on immunofluorescence imaging of chemokine receptor expression.

Results: Initial infection events are widespread and vary between animals. We identified SIV infected cells by immunofluorescence staining of viral proteins Gag and Env, first in infected macaque PBMC, then throughout the female reproductive tract. Th17 cells (CCR6+ CCR10-) represent a particularly vulnerable mucosal population, concordant with their rapid infection and depletion in the gut. In a focus of infection, as many as 75% of infected cells have a Th17 phenotype, but represent only a minority of total T cells present. Accordingly, we find the pro-inflammatory cytokine IL17 is produced near many foci of infection. Alternately, CCR10+ cells, potentially immature dendritic cells, can also contain viral proteins. In the vaginal vault, infection occurs primarily in T cells below the basement membrane of the epithelium. Infection occurs in both single cells and immune aggregates comprised of several dozen cells. In ovarian tissue, infected cells are found in close proximity but we do not find aggregates.

Additionally, in foci of vaginal infection we amplified single copies of proviral gag and examined their sequences for evidence of APOBEC3G induced mutation. Early after transmission, we find no evidence of APOBEC3G activity illustrating the effectiveness of Vif in vivo.

Conclusions: Collectively through these studies we are able to observe the earliest events after viral acquisition that dictate the early pathogenesis of SIV infection. The virus has a preference for the Th17 subset. This knowledge along with the nature of the host response to infection can better inform the rational design of prevention strategies.
Title: TRANSCRIPTIONAL REGULATION OF CORTICOTROPIN RELEASING FACTOR GENE EXPRESSION

Summary: Corticotropin-releasing factor (CRF) has been well established as a key mediator of stress responses and voiding control, where increased CRF levels in Barrington’s nucleus induce urinary retention and bladder dysfunction. Arachidonic acid (AA) metabolites have been shown to modulate CRF expression, however the transcriptional mediators of this modulation are unknown. We are investigating the role of PPRE and XRE sites on CRF gene expression.

Objective:
Determine the role of PPAR and Ahr in AA-dependent CRF induction.

Methods:
We used MIRAGE software to identify candidate transcription factor binding sites in a 1kb region of the human CRF gene promoter. We identified a peroxisome proliferator-activated hormone response element (PPRE) and two Xenobiotic Responsive Element (XRE) sites as candidate mediators of AA-dependent CRF induction. Site-directed mutations of the PPRE and XRE sites were generated in a CRF-luciferase reporter plasmid. We evaluated expression of WT and the mutants in HEK 293T cells for their responses to AA. We also transfected in transcription factors AhR and PPAR and evaluated AA-dependent CRF induction.

Results:
Mutation of XRE1 resulted in significantly decreased basal CRF expression, while mutation of XRE2 or PPAR had modest effects. However upon AA induction, the PPRE mutant had increased CRF expression compared to WT, whereas XRE1 had decreased expression. The double mutation of XRE1 and XRE2 resulted in decreased responsiveness to AA. Co-transfection with PPAR had modest effects; however, AhR resulted in a significant increase in AA-dependent CRF expression.

Conclusions:
These results suggest AhR binding to the XRE sites modulates AA-dependent CRF gene expression. Continued studies will examine the role of such factors in modulating voiding in response to stress.

Research reported in this publication was supported by the National Institute Of Allergy And Infectious Diseases of the National Institutes of Health under Award Number F31AI106357.
Presenting Author: Suzanne M Schauwecker
Position: MD-PhD Student
Principal Investigator: Charles V Clevenger, MD, PhD
Department: Pathology
Clinical, or Basic Science, or Public Health and Social Sciences: Basic Science, Women’s Health Research
Email: s-wetz@northwestern.edu

Title: HMGN2 Promotes Prolactin-Induced Transcription by Facilitating the Loss of the Linker Histone H1 from Promoter DNA

Summary: The polypeptide hormone prolactin (PRL) is essential for normal breast tissue growth and maturation; however, this hormone also contributes to breast cancer development. PRL binds to and activates the transmembrane PRL receptor (PRLr). The PRLr signals from the cell surface to the nucleus both by activating canonical signals, such as the Jak2/Stat5 pathway, and by directly translocating to the nucleus. We have previously shown that nuclear PRLr binds to the chromatin-modifying protein high-mobility group N2 (HMGN2). The PRLr recruits HMGN2 to the promoter of the PRL-responsive gene CISH (cytokine-inducible SH2-containing protein). At this promoter, HMGN2 stimulates transcription, but the mechanism by which HMGN2 does so is unknown. One potential mechanism previously identified is that HMGN2 binds to nucleosomes and induces chromatin decompaction by competition with chromatin-compacting proteins. Given this, we hypothesized that HMGN2 causes chromatin decompaction at promoters of PRL-responsive genes, allowing the transcriptional machinery to access the promoter DNA and initiate transcription.

Objective: The objective of this study is to determine how PRLr-mediated recruitment of HMGN2 stimulates the transcription of PRL-responsive genes.

Methods: Human breast cancer cells (T47D and MCF7) were utilized for these studies. The CISH promoter was examined by chromatin immunoprecipitation (ChIP) for factors regulating chromatin compaction or transcription. CISH transcription was analyzed by reverse transcription polymerase chain reaction (RT-PCR). The nucleosome landscape at the CISH promoter was mapped using the micrococcal nuclease (MNase) protection assay. Chromatin was digested with MNase, and protected (nucleosome-bound) regions were amplified by quantitative PCR.

Results: PRL stimulation resulted in the loss of histone H1.2 from the CISH promoter. Following HMGN2 knockdown, the loss of H1.2 was attenuated. Therefore, HMGN2 may stimulate CISH transcription by facilitating the loss of H1.2 from the promoter, likely through competitive binding. Consistent with this hypothesis, the decrease in CISH expression induced by HMGN2 knockdown was rescued by the additional knockdown of histone H1.2, further suggesting that the role of HMGN2 in CISH transcription involves the loss of H1.2. Consistent with transcriptional activation, PRL stimulation also resulted in increased RNA Polymerase II (Pol II) bound at the CISH promoter; knockdown of HMGN2 resulted in less bound Pol II. The nucleosome landscape at the CISH promoter was then mapped using the MNase protection assay. Prior to PRL stimulation, the CISH promoter exhibited a bound nucleosome overlying the binding site of the necessary transcription factor Stat5a. PRL stimulation resulted in eviction of this nucleosome. The effect of HMGN2 on the nucleosome landscape at the CISH promoter is being determined.

Conclusions: These data suggest that PRL induces CISH transcription through the coordinated loss of both the linker histone H1.2 and nucleosome core particles. HMGN2 stimulates PRL-induced CISH transcription by facilitating the loss of H1.2 from the promoter, thus allowing Pol II to better access the promoter DNA and drive transcription.
Title: Utilizing Mucin-tethered HIV IgG to Enhance HIV Vaccine Function

Summary: Our lab has recently reported that antibodies can tightly bind mucus found in the female reproductive tract. We have identified several specific interactions between subsets of IgG and specific mucins with the best-defined example being HIV IgG and a fragment of MUC16. MUC16 association with IgG from HIV chronically infected individuals is increased 2-3 fold relative to the binding of IgG from healthy individuals. We have found that the MUC16 associated antibodies are enriched for SIV and HIV binding antibodies.

Objective: The objective of this study is to decipher which sub-population of HIV IgG is important for binding MUC16 and how these antibodies could be used to sequester incoming virions to the mucus and enhance vaccine function.

Methods: To purify human and rhesus IgG that associates with MUC16, we conjugated MUC16 to magnetic beads and performed a capture assay. A subset of IgG bound tightly (nM) to MUC16, requiring denaturation (GuHCl) to remove them from bound MUC16. These antibodies were then interrogated for their antigen specificity through a Luminex bead assay. Antibody effector function was measured through a rapid fluorescent antibody dependent cellular cytotoxicity assay (RFADCC) and FcγR ELISA.

Results: Macaque IgGs were isolated before and after SIV challenge and there was an elevation in MUC16 binding post-infection. The macaque antibodies that bound tightly to MUC16 had elevated binding to gp41, but not gp120. MUC16 binding to HIV IgG increases with disease progression with chronic HIV individuals containing the highest binders. MUC16 associated HIV IgG from chronically infected individuals mirrored the enhanced gp41 antigen specificity seen in macaques underscoring the translatable nature of the two systems. Reduced ADCC and FcγR engagement were observed in these MUC16 associated antibodies. This effector function profile is unique, highlighting Fc specialization.

Conclusions: Understanding the properties of HIV IgG antibodies that bind to mucus will aid our understanding of HIV infection. The observed enrichment of gp41 specific antibodies with MUC16, relative to gp120, suggest that the immune system has the ability to direct specific antigen responses to interact with a specific mucin. This observation reveals that it may be possible to direct vaccine-generated responses to associate with mucins and enhance barrier function. This would increase vaccine function by taking advantage of a new effector function that can facilitate virion trapping in mucus.
Presenting Author: [Oukseub Lee, Ph.D.]
Position: [Postdoctoral fellow]
Principal Investigator: [Seema A. Khan, MD]
Department: [Surgery]
Clinical, or Basic Science, or Public Health and Social Sciences: [Basic Science and/or Women’s Health Research]
Email: [o-lee@northwestern.edu]

Title: Low dose of CDB-2914 and CDB-4124 efficiently inhibit the growth of T47D spheroid induced by pre-menopausal and post-menopausal concentrations of estrogen and progesterone

Background: The anti-progestins (RU-486, CDB-2914 and CDB-4124) may have potential to prevent estrogen receptor (ER) and progesterone receptor (PR) positive breast cancer. Physiological estradiol (E2), and progesterone (P4) levels are different in pre- and post-menopausal women. The purpose of this study was to determine: 1) Whether the physiological female hormones at pre- and postmenopausal concentrations affect the growth of an in vitro model of breast cancer, i.e., T47D spheroids, and 2) Whether anti-progestins at pharmacological concentrations work as growth inhibitors in high and low hormonal environments.

Methods: T47D cells were grown as spheroids in the presence of serum concentrations of E2 and P4 consistent with pre- and postmenopause. Premenopausal luteal phase concentrations were 262 pM (71.3 pg/mL) of E2 + 18 nM (5.66 ng/mL) of P4; postmenopausal concentrations were 122 pM (33.2 pg/mL) of E2 + 3 nM (1.08 ng/mL) of P4. T47D cells (5000 per well) were seeded in 1.5% agarose coated 96 well plates, and grown in phenol red-free mammary epithelial cell growth basal medium (Lonza) supplemented with 10% double charcoal -stripped FBS. Hormones and anti-progestin treatments started 24 hrs after cell seeding. Three concentrations (50, 250, 1000 nM) of the anti-progestins were tested. Images of each spheroid were taken daily for 14 days, and the sizes of spheroids were analyzed by area (Pixel) using ImageJ software.

Results: Premenopausal and postmenopausal hormone concentrations stimulated spheroid growth by two- fold and 1.7 fold higher, respectively, when compared to the vehicle control (0.1% DMSO) at14 days. In the premenopausal condition, RU-486 showed moderate inhibition of spheroid growth at all three concentrations; CDB-2914 was more efficient at inhibition than CDB-4124 at 50 nM. At 250 nM and 1000 nM, CDB-2914 and CDB-4124 showed similar efficacy. In the postmenopausal condition, RU-486 showed very minor inhibition on spheroid growth at all three concentrations; CDB-2914 showed significantly higher inhibition than CDB-4124 at 50 nM. At 250 nM and 1000 nM, CDB-4124 was more efficient than CDB-2914.

Conclusions: Our results indicate that T47D spheroids will grow in postmenopausal hormone concentrations, but growth is enhanced in premenopausal hormone conditions. RU-486 did not produce effective inhibition at postmenopausal hormone levels; however pharmacological concentrations (50, 250 and 1000 nM) of both CDB-2914 and CDB-4124 efficiently decrease the spheroid growth induced by both premenopausal and postmenopausal hormone levels. These data suggest that low doses of CDB-2914 and CDB-4124 should be further investigated for ER/PR positive breast cancer prevention and therapy.

Acknowledgements: This project was supported by the Breast Cancer Research Foundation
Presenting Author: Arangassery Rosemary Bastian, PhD  
Position: Postdoctoral Fellow  
Principal Investigator: Patrick Kiser, PhD  
Department: Biomedical Engineering  
Science: Basic Science  
Email: rosemary.bastian@northwestern.edu  

Title: Complexes between Mucins and IgG Synergistically enhance Antibody Entry Inhibition Activity Against HIV Entry

Summary: Goblet cells in the mucosal epithelia secrete a viscoelastic and lubricating biopolymer composed of highly glycosylated mucins that can oligomerize into large biopolymer structures. These mucins coat the GI, respiratory and female reproductive tract and functions as an innate immune-barrier that microbes and pathogens must transit prior to reaching target cells. Antibodies (Abs) generated against these pathogens by the adaptive immune system are also secreted into this bio-fluid and can interact weakly with the mucins leading to formation of immune complexes with pathogens. We have recently found that antibodies (isotype IgG) can tightly bind to mucins with nanomolar affinity. This tight binding could enhance mucosal barrier function and entrapment of the pathogen in the mucin-gel and via steric repulsion. The current study is aimed to understand the biophysics of this mucin-antibody binding and functional interaction of the mucin-Ab complex with pathogen surface proteins. We will also study how mucin-Ab complex can synergistically increase the activity of the antibody and inhibit viral entry. This work will enhance the understanding of antibody function at mucosal interface and could be an important mechanism of action of mucosal vaccines.

Objective: Studying the mechanism of the mucin-Ab interface and how this plays a role in pathogen entrapment at the mucosal barrier.

Sample: In order to study the mucin-Ab interaction we used MUC5AC mucin subtype mostly found in the female reproductive tract and HIV-1 as the pathogen. MUC5AC was produced in vitro using engineered human colorectal adenocarcinoma (HT29) cells. The antibodies used included a panel of HIV-1 antibodies with differential binding. The HIV-1 virus used was the lab adapted BaL subtype.

Methods: Initially to understand the mucin-Ab complex interaction we used advanced biophysical methods including surface plasmon resonance to study binding kinetics and isothermal calorimetry (ITC) to study the thermodynamics of binding. The mucin-Ab complex was then subjected to various HIV-1 infection inhibition assays to understand the mucin-Ab complex function in preventing entry into host cells. To better understand the interactions of HIV with the mucin-Ab complexes we used immunohistochemistry and light scattering.

Results: The mucin-Ab complex showed strong binding kinetics resulting in nanomolar binding constants (Kd). The intrinsic thermodynamic parameters obtained for mucin-Ab binding was highly favorable with low negative enthalpy showing strong secondary binding events and conformational changes. ITC also showed that the mucin-Ab binding stoichiometry was approximately one mole of mucin to eight moles of antibody. The antiviral assays showed that the mucin-Ab complex lead to increased potency of infection inhibition compared to Ab alone with some Abs showing over 200 fold potency enhancement when complexed with mucin.

Conclusions: Our study therefore has established that the mucin-Ab interaction is strong and results in a advanced complex formation. Further we have shown that mucin-Ab complex results in HIV-1 synergistically increase functional activity of the Abs as entry inhibitors. This work will enhance the understanding of antibody function at mucosal interface and provide a potential new mechanism of action for mucosally active vaccines against pathogens like HIV, influenza and HPV.
Title: Identification of deleterious small variants in families affected by polycystic ovary syndrome

Authors: Dapas ML, Sisk RK, Armstrong LL, Urbanek M, Dunaif A, Hayes MG.

Summary: Polycystic ovary syndrome (PCOS) is a highly heritable and complex disease that affects 7% of premenopausal women. Common genetic susceptibility variants that have been mapped for PCOS confer very small increases in disease risk and fail to account for the observed heritability (~78%). Rare variants with larger biological effects may be responsible for the remaining heritability gap and may contribute more significantly to the development of PCOS. We performed whole genome sequencing on 76 two-generation families (average size = 4.2 individuals) with multiple daughters affected by PCOS, and filtered for corresponding rare variants that were predicted to have deleterious effects based on the Combined Annotation Dependent Depletion (CADD) tool. These variants were then burden tested at the gene level for associations with PCOS and its quantitative traits. After adjusting for variables such as CADD score cutoff, patterns of variant inheritance, minor allele frequency, burden testing region demarcation, and variant call quality, we can identify phenotypic associations with rare deleterious variants, and prioritize regions of interest for follow-up study. Preliminary results identified accumulations of rare deleterious variants that significantly associate with high testosterone levels, one of the core reproductive phenotypes of PCOS. Additional testing will be required to verify whether rare variants thus identified contribute to the pathogenesis of PCOS.
Title: Therapeutic Advantage of Intrabeam IORT for Treating Shallowly Populated Breast Cancer Lesions

Summary: Radiotherapy is a major part of the standard of care for patients with breast cancer after breast conserving surgery. In this study, the therapeutic advantage of intrabeam intraoperative radiotherapy over more traditional external beam radiotherapy was elucidated using radiobiological models. It was found that intrabeam IORT has a sizeable therapeutic advantage over EBRT.

Objective: The purpose of this study was to use radiobiological models to predict the therapeutic impact of intrabeam intra-operative radiation therapy (IB-IORT) for treating breast cancer after lumpectomy compared to traditional external beam IORT such as Mebetron-based IORT, for different prescription doses and cancer cell distributions within the remaining tissue.

Methods: Based on the commissioning data, the three dimensional (3D) radiation doses of IORT using a 4-cm diameter spherical applicator at the energy of 50 keV were calculated. The cancer cells were assumed to have different depths of infiltration and populated with different density distribution after surgery. The modified linear quadratic model (MLQ) was used to estimate the radiobiological response of the tumor and interspersed normal cells with different radio-sensitivities. The equivalent uniform dose (EUD) of the treatment was calculated for two types of breast cancer cells (acutely responding and slow responding), and three types of normal cells (radiosensitive, moderately radiosensitive, and radioresistant). A prescription dose of 8, 10, 15, 20, and 25 Gy was prescribed at the applicator surface. Cancer cell distributions in the postsurgical tissue field were assumed to follow a Gaussian distribution with a standard deviation of 0.5, 1.0, 2.0, 3.0, and 5.0 mm, which corresponded to a depth of infiltration of 1.5, 3.0, 6.0, 9.0, and 15.0 mm, respectively. A maximum cancer cell percentage of 10%, 1%, and 0.1% at the surface were respectively tested. By comparing the average survival fraction of normal cells in the IB-IORT therapy and at the EUD, the therapeutic ratios (TRs) were calculated.

Results: The EUDs were found to be dependent on the distributions of cancer cells, but only minimally dependent on the cancer cell radio-sensitivities and independent of the density of cancer cells at the surface. For a prescription dose of 20 Gy, EUDs are 17.51, 16.11 and 12.96 Gy respectively for 0.5, 1.0 and 2.0 mm for the standard deviation of Gaussian distributions. The TR was found to be strongly dependent upon cancer distributions and cancer cell radio-sensitivities and weakly dependent on the cancer cell density. At the above standard deviations of Gaussians and 1% cancer cell density at the surface, TRs were 2.59, 25.68 and 57.44 for the acutely responding breast cancer, and 2.52, 21.94 and 45.26 for the slow responding breast cancer. When the surface cancer cell density decreased from 10% to 0.01%, TR only decreased by 3%. The IB-IORT favors the acutely responding breast cancer cells inside radiosensitive normal tissues. For the varying doses, similar results were found, but as dose increased, both EUD and TR increased as well.

Conclusions: IB-IORT provided a pronounced therapeutic advantage in maximally killing cancer cells and sparing normal cells as compared to that seen with single fraction, open uniform EB-IORT. This would decrease radiation related complications of the treatment and even cosmetic impacts. IB-IORT should be considered as the first choice among all types of IORTs for post breast conserving surgery treatment.
Title: Development of a 3D bioengineered uterus

Summary: The human uterus is a dynamic organ of the female reproductive tract that is extensively remodeled in response to the ovarian steroid hormones; estrogen and progesterone. Model systems for human uterine physiology are limiting and not always translatable, especially in the context of uterine diseases.

Objective: The goal of this study was to create a novel 3D model of the uterus that will lead to a better understanding of the physiologic and pathophysiologic processes.

Results: A three-dimensional uterine scaffold was generated, by the method of decellularization of endometrial and myometrial tissue using 0.1% SDS for 5-7 days. The final decellularized scaffold was devoid of any cellular material but maintained the 3D architecture of the tissue and preserved the extracellular matrix proteins. The presence of fibrous proteins including collagen I & IV, laminin and fibronectin were confirmed by immunohistochemistry staining. Primary human endometrial stromal and epithelial cells were isolated following tissue digestion and expanded separately on 2D plates and then cultured on the decellularized endometrium scaffold. The 3D myometrium was established in a similar manner by seeding human primary myometrial cells on decellularized myometrium or leiomyoma scaffolds. Hematoxylin and eosin staining confirmed that the cells were present throughout the decellularized matrix after only one day in culture. Immunohistochemistry detected the presence of vimentin and cytokeratin positive cells. Estrogen and progesterone receptors were expressed in a subset of cells within the glands and stroma of the endometrium. The expression of estrogen and progesterone receptors was evenly apparent in the majority of the cells within the myometrial scaffold. Interestingly, there was a higher expression of progesterone receptor than estrogen receptor on myometrial cells seeded on leiomyoma scaffold.

Conclusion: In summary a novel 3D uterine culture system comprised of endometrium and myometrium that express steroid hormone receptors has been developed. This model will significantly aid in the understanding hormonal regulation of the human uterus and can be used towards the advancement of treatment options for uterine diseases.
Title: Progesterone receptor (PR) blockade by antiprogestin CDB4124 in hormone receptor positive breast cancer cells leads to significant inhibition of G2/M cell cycle genes

Background: Several lines of evidence suggest that progesterone signaling is important in the breast cancer development. One way to probe the effects of progesterone in both normal and malignant breast tissue is to block its action. Older antiprogestins are non-specific in that they have high anti-gucocorticoid activity in addition to their anti-PR activity. In this study, a new anti-progestin CDB4124 (telapristone), which has low anti-gucocorticoid activity, was evaluated for its effects on cell proliferation, cell cycle progression, and the binding of PR to the progesterone receptor response element. We also sought to identify a PR related gene signature in hormone receptor positive (ER+, PR+) breast cancer cells in order to identify lesions that may be responsive to PR blockade.

Methods: T47D cells were analyzed for the proliferation, cell cycle, PRE promotor activity in the presence of hormones and CDB4124 using MTT assay, flow cytometry and the Dual-Luciferase® Reporter Assay System. Gene expression array was performed to identify genes regulated by progesterone receptor and inversely affected by CDB4124. 16 genes were selected and their expression was validated using Real-Time PCR System.

Summary of results:

1. T47D cell proliferation increased 1.5 fold upon treatment with P4, and 2 fold upon MPA or R5020 treatment both alone or in combination with E2 after 24 hours. This increase was blocked by 50% in the presence of CDB4124 (0.1µM and 1µM).
2. Upon treatment with P4, MPA and R5020 alone or in combination with E2 T47D cells showed significant increases in S and G2/M phases and decreases in G0/G1, which could be blocked by CDB4124 (p<0.05).
3. The PRE reporter activity resulting from P4, MPA and R5020 stimulation in different breast cancer cell lines that express PR (T47D, BT474 and MCF-7) was inhibited by 80-90% in the presence of CDB4124 (10 to 1000nM) (p< 0.001).
4. GeneGo Metacore analysis revealed significant enrichment of cell cycle pathways (FDR, p<1.0X10-11) upon treatment of T47D cells with R5020. Furthermore, addition of CDB4124 to R5020 treated T47D cells showed inhibition of the same cell cycle pathways (FDR,p<1.0X10-14).
5. A G2/M relating 16-gene panel that was selected based on >1.5 fold up-regulation (p<0.001) and on the blockade by CD4124 during treatment with R5020(10nM) was validated by qPCR (≥1.5, p<0.05). MCF10A cells showed negligible response to PR ligand (no significant up-regualtion in 16 genes), which is ascribed to the lack of PR.

Conclusion: Our data demonstrate that PR-mediated cell proliferation in hormone receptor positive breast cancer cells treated with three different PR ligands can be blocked by CBD4124, which additionally down-regulates key genes involved in the G2/M phase of the cell cycle.
Title: Efficacy of a TDF intravaginal ring in a pigtail macaque model of simian-HIV infection

Summary: Human Immunodeficiency Virus (HIV) causes Acquired Immune Deficiency Syndrome (AIDS). Approximately 34 million people are currently infected with HIV worldwide. There is no cure for HIV and the virus continues to be a significant cause of global mortality with a total of 24 million accumulated AIDS-related deaths to date. Highly Active Antiretroviral Therapy (HAART) reduces viral load and leads to prolonged survival. Though oral pre-exposure prophylaxis efficiently prevents HIV transmission, the main obstacles of this treatment are common side effects such as nausea, diarrhea, pain, headache, depression etc. To overcome adverse effects caused by systemic distribution of antiviral drugs a novel antiretroviral medical device, the intravaginal ring (IVR) was developed to prevent sexual transmission of HIV in the female reproductive tract (FRT). In this study we examine the tenofovir disoproxil fumarate intravaginal ring (TDF IVR) in vivo. Our data show that TDF IVR does not completely protect pigtail macaques from a single simian-HIV challenge.

Objective: Our previous studies demonstrated viral infection throughout the female reproductive tract. The aim of this study is to examine if TDF IVR protects the entire FRT in pigtail macaques, and to determine localization and phenotype of infected cells.

Methods: Pigtail macaque model was chosen to study efficacy of the TDF IVR. Single-round infectious reporter virions for luciferase and mCherry expression were generated. High dose of this virus was used for a single vaginal challenge of 7 pigtail macaques that were treated with the TDF IVR for 25 days. Three days later animals were euthanized, IVRs were removed and the entire FRT was isolated for analyses of viral infection. To determine localization of infection the tissue was first soaked in luciferin to examine luciferase expression using in vivo imaging. Fluorescent microscopy was used to find first transduced cells expressing reporter genes such as luciferase and mCherry, as well as to determine the phenotype of infected cells. Furthermore, we optimized the nested PCR method to confirm the presence of proviral DNA.

Results: In vivo imaging demonstrated luciferase activity in ovaries of two animals that had the TDF IVR. Transduced cells expressing luciferase and mCherry genes were found in these ovaries and phenotyped. Infected cells were shown to be CD4 expressing cells. Search for transduced cells in other ovaries is ongoing. Nested PCR was optimized to detect a single copy of proviral DNA in infected cells. Using this highly sensitive PCR method screening of the entire FRT of all pigtails is in progress.

Conclusions: In this study we show that TDF IVR did not completely protect pigtail macaques from a single simian-HIV challenge. Single infected cells were found in ovaries of a TDF IVR treated pigtail macaques. This ongoing work will show if TDF IVR protects other parts of FRT from viral infections. We further suggest assessing efficacy of this device against tenofovir resistant mutants such M41L. This study will help to gain important insights regarding the safety of this device prior to use in women.
Title: Aromatase Gene Expression is Upregulated in Diagnostic Muscle Biopsies from Girls with Untreated Juvenile Dermatomyositis

Dong Xu, MD1, 2; Akadia Kachaochana, BS1; Adam Ostrower, BS1; John S Coon, V, BS3; Gabrielle A. Morgan, MA1; Hong Zhao, MD, Ph.D3; Chiang-Ching Huang, PhD4; Serdar E Bulun, MD3; Lauren M. Pachman, MD1, 2

Ann & Robert H. Lurie Children’s Hospital of Chicago Research Center, Program of Excellence in Cure-Juvenile Myositis (JM) Research, Northwestern University Feinberg School of Medicine1. Department of Pediatrics, Division of Rheumatology2, Department of Obstetrics and Gynecology3, Northwestern University Feinberg School of Medicine, Chicago, IL. Department of Preventive Medicine4, University of Wisconsin at Milwaukee, Milwaukee, WI

Background: We observed: WT-1 was massively hypomethylated in muscle biopsies (MBx) from untreated or treated active JDM. Others had shown: 1) WT-1 controls the proximal promoter II activity of aromatase, which regulates estrogen synthesis; 2) proinflammatory cytokines elicit aromatase production through its distal aromatase promoter I.4.

Hypothesis: Dysregulated estrogen homeostasis may play a role in JDM pathophysiology.

Methods: Ten girls (5 regular, 5 irregular menses) with JDM had MRI-directed IRB-consented MBx (mean age 9.0±3 yrs) were compared with MBx from 4 orthopedic control girls (16.0±1.0 yrs). Muscle total RNA was assayed for aromatase gene expression levels, qPCR (Taqman). Mesoscale measured plasma levels of proinflammatory cytokines (IL6, IL-1β and TNF-α, t test). The association of the level of aromatase gene expression with disease activity scores (DAS) for skin, muscle, and total score was determined.

Results: Aromatase mRNA levels were 9.78 fold higher in JDM MBx compared with healthy controls (p=0.004), but did not differ between JDM girls with either regular or irregular menses (p=0.4). Aromatase levels were not associated with any DAS. Promoter I.4 was the dominant aromatase promoter identified in JDM MBx. In JDM plasma, IL-6, IL-1β and TNF-α levels were elevated compared to controls (p<0.05).

Conclusion: Aromatase upregulation may be associated with JDM pathophysiology. We speculate: 1) elevated proinflammatory cytokines induce aromatase expression via the distal aromatase promoter I.4 in JDM; 2) high aromatase leading to increased local estrogen biosynthesis in muscle tissue may contribute to the targeted distribution of muscle involvement characteristic of JDM.
Title: A Cost-effectiveness Analysis of Morcellation Hysterectomy for Fibroids

Study Objective: To estimate the cost-effectiveness of eliminating morcellation in the surgical treatment of leiomyomas from a societal perspective.

Measurements: A decision analysis model was constructed using probabilities, costs, and utility data from published sources. A cost-effectiveness analysis analyzing both quality-adjusted life years (QALYs) and cases disseminated cancer was performed to determine the incremental cost-effectiveness ratio (ICER) of eliminating morcellation as a tool in the surgical treatment of leiomyomas. Costs and utilities were discounted using standard methodology. The base case included health care system costs and costs incurred by the patient for surgery-related disability. One way sensitivity analyses were performed to assess the effect of various assumptions.

Main Results: A strategy of non-morcellation hysterectomy via laparotomy cost more ($30,359.92 versus $20,853.15) and yielded more QALYs (21.284 versus 21.280) relative to morcellation hysterectomy. The ICER for non-morcellation hysterectomy compared to morcellation hysterectomy was $2,184,172 per QALY. The cost to prevent one case of disseminated cancer was $10,540,832. Health care costs (prolonged hospitalizations) and costs to patients of prolonged time away from work were the primary drivers of cost differential between the two strategies. Even when the incidence of occult sarcoma in leiomyoma surgery was ranged to twice that reported by proponents of banning morcellation (0.98) the ICER for non-morcellation hysterectomy was $644,393.30.

Conclusions: Eliminating morcellation hysterectomy as a treatment for fibroids is not cost-effective under a wide variety of probability and cost assumptions. Performing laparotomy for all patients who might otherwise be candidates for morcellation hysterectomy is a costly policy from a societal perspective.
Title: Placentophagy: Perspectives and Practice Amongst Prentice Patients

All Authors: Schuette, S., Brown, K., Cuthbert, D., Coyle, C., Clark, C. T.

Summary: Human placentophagy, consumption of the placenta postpartum, has recently been popularized in the media with advocates reporting that ingesting the placenta provides hormones, chemical elements, and endogenous opioids that alleviate postpartum complications including depression, lactation problems, iron deficiency, and pain (Beacock, 2012, Selander et al., 2013).

Objectives: This study investigated (1) patients’ awareness, perceptions, attitudes and beliefs toward placentophagy, (2) whether health care providers and patients engage in conversations about placentophagy, (3) which patients are choosing placentophagy and (4) methods of current practice.

Sample: The sample included 153 female patients between the ages of 19-57 years old (Mean: 32.71). Participants self-identified as primarily Caucasian (65.8%) or African American (15.8%). The vast majority (76.3%) of participants were married and 84% had been pregnant before.

Methods: The study consisted of 1 non-blinded cross-sectional survey that was distributed at Northwestern Hospital to obstetric patients in the postpartum unit of Prentice Women’s Hospital and psychiatry patients in a women’s mental health clinic, The Asher Center for the Study and Treatment of Depressive Disorders.

Results: Of women surveyed (n=153), 66.2% (n=100) said they had heard of placentophagy, 12.5% (n=19) were willing to try placentophagy, but only 1.3% (n=2) had pursued it. The majority (30.1%) heard of the practice through the media. Approximately three times the number of patients (26.17%) believed there were benefits to placentophagy than those who perceived there were risks (8.49%), citing reduced postpartum depression as the most common benefit, followed by increased healing postpartum, increased energy, and nutritional benefits. When asked about what measures they would consider for prevention/treatment of post-pregnancy complications, 29.5% of patients were equally willing to try either placentophagy or medication, 23% were not willing to try placentophagy but would try medication, and 25.9% would not consider either method. The vast majority said either “yes” (36.1%, n=52) or “maybe, not sure” (52.1%, n=75), healthcare providers should discuss placentophagy with their patients.

Conclusions: Women are choosing placentophagy and reporting multiple benefits despite the lack of empirical evidence of therapeutic efficacy. More research examining the actual content of placenta tissue and capsules is necessary in order to determine the true potential benefits, and risks, of this practice.

Title: HYPERTHERMIA AND RADIATION THERAPY FOR LOCALLY ADVANCED OR RECURRENT BREAST CANCER

Objective:

This study aims to report the long-term treatment outcomes and toxicities of combined hyperthermia (HT) and radiation therapy (RT) in treatment of locally advanced, or loco-regionally recurrent breast cancer.

Patients and Methods:

After obtaining IRB approval, records of patients with locally advanced or loco-regionally recurrent breast cancer treated sequentially with HT and RT from January 1991 to December 2007 were reviewed. Planned RT doses were >40 Gy in retreatment patients and >60 Gy in RT naïve patients. Each HT site was planned for 2 sessions/week for >4 sessions. Superficial or interstitial applicators were used. Superficial or implanted thermistors measured intra-tumoral temperature. Thermal equivalent dose (TED), defined by number of minutes at >42.5°C and >43°C, was calculated for each site and for the entire course. Endpoints of analysis were treatment response, local control and survival.

Results:

The study included 127 patients who received hyperthermia to 167 sites. Treated sites were intact breast (24.4%), chest wall/skin (67.7%), and breast/chest wall and nodes (7.9%). At a median follow-up of 13 months (mean 30±38, range 0-182), improved overall survival was significantly associated with increasing RT dose (p<0.0001), median TED 42.5°C ≥ 200 minutes (p=0.003), and local control (p=0.0002). Local control at last follow-up was seen in 55.1% of patients. Complete response significantly associated with median TED 42.5°C ≥ 200 minutes (p=0.002) and median TED 43°C ≥ 100 minutes (p=0.03). Grade 3 or 4 Telangiectasia, desquamation, ulceration, fibrosis, and abscess formation were reported in 4.7%, 24.4%, 6.7%, 6.3%, and 0.8% of patients respectively, while 43.3% of patients did not report any grade 3 or 4 toxicity.

Conclusions:

HT and RT is an effective combination in obtaining local control in a group of patients that have been historically difficult to treat by RT. Overall survival was related to the ability to obtain local control, higher doses of RT, and HT.
Title: Request and fulfillment of post-partum tubal ligation in patients after high-risk pregnancy

Summary: A retrospective chart review of 3063 women delivering at a university hospital in 2009-2010 was conducted to determine whether high-risk pregnancy status influenced request for post-partum tubal ligation or subsequent completion of the procedure.

Objective: This study seeks to establish whether obstetric or medical risk status influences patients' request for or subsequent completion of PPTL.

Sample: The study sample included 3063 pregnant women delivering at a university hospital in 2009-2010.

Methods: This was a retrospective study of women delivering at a university hospital in 2009-2010 who received prenatal care in the faculty and resident clinics. High-risk status was defined by SMFM guidelines. Documentation of contraceptive plan and administration of contraceptive methods was abstracted from patient records. Subsequent pregnancies through March 1, 2013 were abstracted.

Results: Of 3063 participants (2048 low-risk and 1015 high-risk), 231 requested PPTL (7.5%). This was more likely among high-risk patients than low-risk (10.0% vs. 6.3%, p<0.001), those with public insurance (13.8% vs. 3.2%, p<0.001), and those with an unintended index pregnancy (13.8% vs. 4.1%, p<0.001). 118 (51.1%) of patients requesting PPTL underwent the procedure immediately postpartum, and 15 received the procedure later in the follow-up period. Successful completion was not associated with race, insurance status, high-risk status or parity. Among 113 women with an unfulfilled PPTL request, there were 17 subsequent pregnancies (15%) during the 27 months of follow up.

Conclusions: Though women with high-risk pregnancies were more likely to choose PPTL, they were not more likely to successfully complete the procedure. In fact, over one-third of high-risk patients' requests were unfulfilled, indicating that significant barriers remain.
Title: THE PAIN ASSOCIATED WITH ALLERGIES IN A FEMALE PELVIC MEDICINE AND RECONSTRUCTIVE SURGERY CLINIC

Summary: Chronic pain conditions such as Interstitial cystitis (IC/PBS) are associated with other chronic pain conditions including fibromyalgia (FM), Irritable bowel disease (IBS), vulvodynia, endometriosis, chronic fatigue syndrome (CSF) and migraines. Central sensitization is a process of the nervous system which results in enhanced responsiveness of the central neurons to input from receptors. This hypersensitivity has been postulated as a theory to explain the symptoms in chronic pain syndromes. It is plausible that if hypersensitivity plays a role in many of the overlapping pain conditions, it could also account for sensitivity to medications, leading one to have multiple medication allergies.

Sample: Women presenting for pelvic floor care.

Objective: We aim to determine if self-reported medication allergies are more common among women with pain diagnoses than women without pain diagnoses presenting for pelvic floor care.

Methods: We performed a retrospective cohort study of new patients presenting to a female pelvic medicine & reconstructive surgery (FPMRS) specialist over 1 year at a tertiary care academic institution. Consecutive new patients were identified from billing records. Electronic medical records were reviewed and demographic information, primary pelvic floor diagnoses, pain diagnoses and self-reported medication allergies were collected. We identified the following pain conditions from the initial visit: interstitial cystitis/painful bladder syndrome (IC/PBS), chronic pelvic pain, vulvodynia, dysmenorrhea, endometriosis, irritable bowel disease, fibromyalgia, myofascial pain, and migraines. Total number of allergies and pain diagnoses were calculated. Chi-squared and Mann-Whitney U tests were used to compare categorical and continuous variables respectively.

Results: Of the 1520 women presenting for pelvic floor care 153 (10%) reported three or more allergies. Three hundred thirty-three women (22%) had at least 1 pain diagnosis with 46 (14%) of these women having IC/PBS. Three or more allergies were more common in women with any pain diagnosis and IC/PBS compared to women without pain (20.7% and 21.7% versus 7.1 % p<0.0005). Women with at least one pain diagnosis were more likely to be younger (p <0.001) and to report more allergies (p<0.001). Likewise those diagnosed with IC/PBS were more likely to be younger (p<0.001), report more allergies (p<0.001), carry more pain diagnoses (p<0.001), and be smokers (p<0.001). The total number of pain diagnoses was also weakly correlated with the number of self-reported allergies (Spearman's correlation coefficient 0.183, p<0.001).

Conclusion: Excessive medication allergies are more common in women with urologic and other chronic pain diagnoses. Future studies should determine the relationship between allergies or perceived allergies and urologic pain.
Presenting Author: Joseph B. Bavaro, MD
Position: Resident, PGY-4
Principal Investigator: Jeanette R. Bauchat, MD
Department: Anesthesiology
Clinical, or Basic Science, or Public Health and Social Sciences:
Clinical / Women’s Health Research
Email: joseph.bavaro@northwestern.edu

Title: Comparing the level of sedation in women undergoing scheduled versus unscheduled cesarean deliveries: a prospective observational study

Intro: UNICEF and the WHO encourage “skin-to-skin” and breastfeeding within the first hour of life because it confers health benefits to the neonate. 1 Hospitals strive to achieve “Baby-Friendly” status which requires breastfeeding within a half hour of birth. 2 Neuraxial anesthesia and prolonged labor may increase levels of sedation during unscheduled cesarean deliveries, which may preclude safe early skin to skin contact. 3,4 We hypothesized that women undergoing unscheduled cesarean delivery (UCD) would self-report greater sedation than those undergoing scheduled cesarean deliveries (SCD).

Methods: A total of 44 healthy women were enrolled: 25 SCD with spinal anesthesia and 19 UCD with epidural anesthesia. At baseline and 15, 30, 45, 60 min intervals after a T4 sensory level was achieved, women reported a numeric rating scale (NRS, 1 to 10) for sedation. The Observer’s Assessment of Alertness and Sedation (OAAS) was assessed at the same intervals. Subject characteristics, surgery duration, time of birth and opioids/benzodiazepines were recorded. NRS and OAAS scores were compared within subjects using Friedman’s test and between subjects using the Mann-Whitney U test. A \( P < 0.01 \) was required to reject the null hypothesis.

Results: NRS for sedation was increased from baseline at all-time points in both group \( (P=0.004) \), and was higher in the UCD compared with the SCD group at baseline, 30, 45 and 60 min. OAAS scores decreased from baseline in both groups \( (P<0.002) \), but were not different between UCD and SCD groups at any time. More UCD (52%) received opioids/benzodiazepines than SCD (20%) \( (P=0.05) \). Mean surgical duration was not different, SCD 42 min (IQR 31-52) and UCD 43 min (IQR 34-51). Mean delivery time was longer in SCD 8.5 min (IQR 7-11) than UCD 7 min (IQR 5-9).

Conclusion: Parturients undergoing UCD were more sedated than those having SCD by self-reported NRS at baseline and during the procedure. Neuraxial anesthesia, maternal exhaustion and sedating medications may be limiting factors to initiating skin to skin and breastfeeding safely in the operating room during UCD.

Title: The Illinois Parental Notification of Abortion Law Impact on the Proportion of Minors Presenting to a Public, First-Trimester Abortion Clinic

Summary: On August 15th 2013, Illinois became the 38th state to require parental involvement in a minor's decision to have an abortion by enacting the Illinois Parental Notification of Abortion Act of 1995 (750 ILCS 70). The law requires abortion providers in Illinois to give at least 48 hours notice to an adult family member prior to performing an abortion for a pregnant minor. The basis for such laws is frequently cited as a means to improve family communication and avoid excluding parents from important reproductive health decisions while opponents argue such laws limit teenagers access to abortion services and by requiring parental involvement may lead to family violence. Prior literature reports the dominant impact of parental involvement laws is an increase in minors traveling outside of their home states to obtain abortion services in states that are less restrictive. We sought to evaluate the impact of one such law in a state surrounded by states with similar, if not more restrictive laws.

Objective: To study the impact of the Illinois Parental Notification of Abortion Act on minors presenting for first trimester abortion at an urban clinic in Chicago, Illinois.

Methods: This study was a descriptive, retrospective review, utilizing a pre-post test design, comparing the proportion of minors undergoing first trimester termination of pregnancy at the Reproductive Health Services (RHS) Clinic at John H. Stroger, Jr. Hospital of Cook County in the 12 months before (August 15, 2012 to August 14, 2013) and the 12 months following (August 15, 2013 to August 14, 2014) the enactment of the Illinois Parental Notification Act. Number of minors, demographic information, gestational age, medical versus surgical abortion, and long-acting reversible contraception (LARC) usage were compared before and after the law. Notification type and person notified for Parental Notification were also reviewed. Older teenagers ages 18 to 21, unaffected by the law, served as a control group. Chi-square tests and t-tests were performed, where appropriate. SAS 9.3 (Cary, NC) was used for data analysis.

Results: Before the law, 320 minors received services of 5,505 total patients (5.8%) and after introduction, 311 minors received services of 6,311 patients (4.9%) (P=0.003). There was a 2.9% decrease in procedures among minors before and after the law, compared to a 15.7% growth in procedures among non-minors. 80.1% of minors notified immediately over the phone at time of scheduling and 86.7% notified via their mother. Among minors, there was no difference in race/ethnicity, age, and mean gestational age before and after the law (P=0.175, P=0.116, and P=0.961). There was an increase (1.6% to 3.4%) in the percentage of minors receiving LARC across the two time periods (P=0.084).

Conclusions: The enactment of a parental involvement law in Illinois did not have a tremendous impact on minors seeking abortion services at a public first trimester clinic, although we did find a lack of a proportional increase procedures among minors compared with older teenagers not affected by the law. Most minors were able to obtain notification immediately at the time of scheduling and notified via their mother.
Title: Increased CD68-Positive Macrophages and CD4-Positive Lymphocytes in Tumor Associated Inflammation in Pregnancy Associated Breast Cancer May Contribute to a Poor Prognosis

Summary: Pregnancy associated breast cancer (PABC), diagnosed during gestation to 5 years post-partum, is associated with a poor prognosis. Those diagnosed within 2 years have an even worse outcome. The microenvironment may be tumor promoting after pregnancy as the mammary gland is remodeled to its pre-pregnant state. In this pro-inflammatory state, CD68+ macrophages promote invasive tumor cell growth and metastases, while CD4+ lymphocytes in breast carcinomas produce high levels of IL-4 which regulate the protumor activities of macrophages. We previously assessed the presence and degree of tumor associated inflammation (TAI) and reported that TAI was more prominent in PABC.

Objective: In this study, our goal was to further characterize the components of TAI in PABC, in particular to see if these tumors were enriched for CD68+ macrophages and CD4+ lymphocytes.

Sample: 38 patients diagnosed with PABC within 2 years of pregnancy (mean=35.5 y/o, range=25-48) and control age-/stage-matched nulliparous women (mean=37.5 y/o, range=29-48) were evaluated.

Methods: Slides were reviewed and pathologic tumor characteristics and TAI were noted. Immunohistochemical stains for CD4, CD8, CD68 and CD137 were performed on 20 PABC and 15 control cases. Extent (1=1-25% positive tumor cells, 2=26-50%, 3=51=75% or 4=76-100%) and intensity (1=weak, 2=moderate or 3=strong) of staining were assessed. A composite score (CS) was calculated by multiplying the extent by intensity. The mean CS of PABC and controls were compared using the Student t-test and a \( p \) value \( \leq 0.05 \) was considered significant.

Results: PABC were more likely than controls to have more CD68+ macrophages (mean CS=10.2 vs. 5.8, \( p<0.0001 \)) and CD4+ lymphocytes (mean CS=10.5 vs. 8.2, \( p=0.016 \)). 80% of PABC had strong immunoreactivity for CD68 (CS= 9-12), while only 27% of controls did (\( p=0.0024 \)). Of interest, among the PABC, 83.3% with the strongest CD68 expression (CS=12) had positive lymph nodes compared to only 25% in those with CS<12 (\( p=0.019 \)). Also, CD8+ lymphocytes (mean CS=9.8 vs. 7.8, \( p=0.05 \)) and CD137+ lymphocytes (mean CS=4.0 vs. 2.4, \( p=0.056 \)) were increased in PABC compared to controls.

Conclusions: 1. The majority of PABC have TAI. 2. Increased CD68+ macrophages are present in PABC. 3. PABC with high expression of CD68 have positive lymph nodes. 4. PABC has more CD4+, CD8+ and CD137+ lymphocytes than controls. Our findings support the role of immunosurveillance in regulating metastatic spread and suggest that TAI, particularly enriched for CD68+ macrophages and CD4+ lymphocytes, may play an important role in tumor progression and metastasis in PABC and contribute to the poor prognosis in these aggressive breast carcinomas.
TITLE: Risk factors for unscheduled 30-day readmission after benign hysterectomy: a multicenter study utilizing the National Surgical Quality Improvement Program database

OBJECTIVE: Readmission rates after hysterectomy have been reported, but specific risk factors for readmission have not been fully delineated. We aimed to determine risk factors for and implications of readmission after hysterectomy utilizing data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).

METHODS: We identified women undergoing hysterectomy for benign disease within NSQIP from 2011 to 2012. Outcomes of interest were 30-day unscheduled readmission rates, variables associated with readmission, and complication and mortality rates associated with readmission. Bivariate analyses were performed using Pearson’s chi-square and independent t-tests, and multivariable regression analysis was performed to identify factors independently associated with readmission.

RESULTS: 21,228 hysterectomies were identified during the study period. 30-day readmission rates were 3.8% for abdominal hysterectomy (AH), 2.7% for laparoscopic hysterectomy (LH), 2.9% for laparoscopic-assisted vaginal hysterectomy (LAVH), and 3.0% for vaginal hysterectomy (VH). Readmission was associated with increased perioperative complications (49.2% versus 6.1%, p<0.001), return to the operating room (OR; 26.3% versus 0.6%, p<0.001), and mortality (0.3% versus 0.01%, p<0.001). The most common complications in patients requiring readmission were surgical site infections (SSI; 28.4%), sepsis (12.8%), urinary tract infection (UTI; 9.7%), and blood transfusion (6.7%). Variables that were independently associated with 30-day readmission after multivariable regression analysis included younger age (OR 0.98 per year, p<0.001), smoking (OR 1.28, p=0.01), diabetes (OR 1.47, p=0.008), dyspnea (OR 1.48, p=0.04), bleeding disorders (OR 1.82, p=0.04), ASA level 3-4 (OR 1.32, p=0.009), prior surgery within 30 days (OR 3.6, p=0.04), longer operative time (OR 1.2 per hour of operative time, p<0.001), inpatient status (OR 1.36, p=0.001), and longer length of hospital stay (OR 1.04 per day, p<0.001).

CONCLUSION: Utilizing a large, nationwide database, we identified several patient-related and procedural risk factors for 30-day readmission after hysterectomy. Readmission was associated with higher rates of return to the OR and a 30-fold increase in mortality. Our findings reinforce the importance of patient selection and optimization of comorbidities prior to hysterectomy. Future research should aim to further delineate differential risks of readmission by surgical route as well as modifiable risk factors for readmission.
Title: Hippocampal Shape Deformity in Breast Cancer Patients With Self-Reported Cognitive Concerns

Summary: Cancer patients receiving adjuvant chemotherapy and estrogen blockade therapy exhibit inward deformation of the hippocampus, predominantly in the bilateral subiculum compared with controls.

Objective: Although advances in breast cancer treatments are improving health outcomes, treatment side effects can be troubling for those undergoing adjuvant chemotherapy. For example, up to 75% of breast cancer patients receiving chemotherapy exhibit cognitive impairment. Neuroimaging studies of this population suggest volume loss in several brain regions including parietal and occipital lobes, yet few studies have performed detailed analysis of the hippocampus, which shows volume loss in animal models of chemotherapy effects. We therefore used high-dimensional deformation mapping analysis to test whether hippocampal shape differs in individuals with breast cancer who received chemotherapy coupled with estrogen therapy versus in healthy controls. To examine whether differences in hippocampal shape were related to cognitive impairment, we tested relationships between these shape abnormalities and performance on standard neuropsychological tests.

Sample: 16 pre-menopausal breast cancer patients and 18 healthy controls. All participants were right-handed, had no history of current or past neurological or psychiatric disorders, denied use of psychoactive drugs. All patients had invasive ductal carcinoma, metastatic lobular carcinoma or inflammatory breast cancer (stages I-IV, histologically confirmed). ECOG (Eastern Cooperative Oncology Group, physician rated) performances grade 0-2 (no-mild physical impairment). Chemotherapy interventions completed within 18 months prior to the study; receiving estrogen blockade therapy (Tamoxifen) at the time of the study.

Methods: Automated high-dimensional deformation mapping (FS+LDDMM) from 3T MPRAGE was used to compare hippocampal shape differences between groups. The NIH Toolbox Cognition Battery was used to measures fluid and crystallized intelligence as well as obtain a total cognition composite. Neuro-QOL self-report was administered to measure anxiety, depression, fatigue, sleep disturbance, and pain levels, as well as perceived executive function and general cognitive concerns.

Results: Significant hippocampal surface deformation $[F(1,31)=6.558, p=0.016]$ after controlling for age $[F(1,31)=1.865, p=0.182]$ in patients compared with controls. Patients showed greater inward deformity. Post-hoc analysis of subfields revealed significant difference in deformity in the subiculum $[F(1,32)=5.669, p=0.023]$. Patients self-reported a greater level of general cognitive concern when compared to controls ($p = 0.004$). No differences between groups for perceived executive function, anxiety, depression, fatigue, sleep disturbance or pain. Patients did not differ from controls in composite measures of objective cognitive function obtained with the NIH Toolbox Cognition Battery. No significant difference in composite fluid cognition $[t(30)=0.291, p=0.773]$, composite crystallized cognition $[t(30)=1.080, p=0.286]$, nor in the overall composite score $[t(30)=1.419, p=0.166]$.

Conclusions: Inward deformation was observed in the subiculum of the hippocampus in breast cancer patients compared with controls, indicating that this region may be particularly vulnerable to the cytotoxic effects of chemotherapy or estrogen blockade therapy. Although patients report more general cognitive concerns, their performance on neuropsychological measures of cognitive function is no different from controls.
Title: Labor Analgesic Intent and the Use of Postpartum Opioids

Summary: Many studies have attempted to identify factors predictive of post-operative analgesic consumption. For example, type of surgery, patient age, and preoperative anxiety may predict postoperative analgesic use. (1) Unfortunately, little is understood about postpartum pain patterns. Some studies have attempted to identify predictors of postpartum pain after cesarean delivery; (2, 3) however, predictors of postpartum pain after vaginal delivery remain poorly characterized. This preliminary study aims to better characterize predictors of opioid use in the postpartum period after vaginal delivery.

Objective: We hypothesized that nulliparous women who anticipated and ultimately received neuraxial labor analgesia would be more likely to use any opioid-based analgesic in the postpartum period compared to nulliparous women who did not anticipate or receive neuraxial labor analgesia.

Methods: Retrospective cross-sectional study. Electronic medical record data on all index vaginal deliveries over a 3-year period at Northwestern Memorial Hospital were extracted. On admission, patients self-identified their race/ethnicity, marital status, and anticipated analgesic use for labor. Extracted data included age, race/ethnicity, primary language, insurance status, gravidity, anticipated labor analgesic use and postpartum analgesic use. Patients were categorized into four groups based on anticipated and actual use of neuraxial labor analgesia. The primary outcome was the postpartum use of any opioid-based analgesics. We conducted initial bivariate analyses and estimated a multivariable logistic regression model of postpartum analgesic use after univariate selection using a P<0.1 for model entry.

Results: A total of 9,030 patients were included in the analysis. After controlling for confounding variables, women who did not anticipate or use neuraxial labor analgesia were less likely to use any opioid-based analgesics in the postpartum period than women who anticipated and used neuraxial labor analgesia (adjusted odds ratio [aOR] 0.44, 95% CI: 0.38 to 0.52). Women of Asian ethnicity were less likely to use postpartum opioids (aOR 0.79, 95% CI: 0.65 to 0.96), while women over 35 years of age were more likely (aOR 1.21, 95% CI: 1.11 to 1.33), after controlling for confounders.

Conclusions: Nulliparous women who anticipate and ultimately use neuraxial labor analgesia are more likely to use postpartum opioid-based analgesics compared to nulliparous women who did not anticipate and did not use neuraxial labor analgesia. These findings suggest that analgesic intent may influence postpartum analgesic consumption. Future work should validate this association.

1. Anesthesiology 2009; 111:657–77
3. Anesthesiology 2013; 118:1170-9
Title: P16 Expression and Biologic Behavior of Flat Vulvar Low-Grade Squamous Intraepithelial Lesions (LSIL)

Summary: Flat vulvar LSIL (vulvar intraepithelial neoplasia grade 1 [VIN 1], “flat condyloma”) is an uncommon entity with poorly understood biologic behavior. Current recommendations endorse treating all vulvar LSIL conservatively, with some controversy as to whether VIN 1 represents a true biologic entity. However, a significant proportion of VIN 1 has been shown to harbor high-risk HPV, with an as yet unclear rate of progression to higher grade squamous lesions. We aimed to better characterize the biology of flat vulvar LSIL, as well as assess a potential prognostic role for the biomarker p16 (overexpressed in high-risk HPV-related lesions) for subsequent development of HSIL.

Objectives: Determine the frequency of p16 positivity in flat vulvar LSIL and the rate of progression of flat vulvar LSIL to higher grade vulvar squamous lesions. Assess the utility of p16 as a prognostic marker in flat vulvar LSIL.

Methods: All available surgical pathology cases (H&E slides) of flat vulvar LSIL from 2003-2010 were reviewed by two pathologists for confirmation of diagnosis. Each case with sufficient material was stained with a p16 immunohistochemical stain (Biocare, clone G175-405). Clinical data and subsequent pathology results were obtained from medical records. The frequency of subsequent development of a vulvar high-grade squamous intraepithelial lesion (HSIL) or invasive squamous cell carcinoma was compared between p16(+) (diffuse block reactivity) and p16(-) (all other expression patterns) cases using the Fisher exact test.

Results: 29 cases of flat LSIL were identified, with a patient age range of 22-65 years (median 39 years). 2 of 29 cases (7%) showed p16 positivity. Follow-up data was available in 22 cases (follow-up range 0.4-132.9 months, mean 52.7 months). 1 of 2 p16(+) cases and 0 of 20 p16(-) cases with follow-up developed subsequent vulvar HSIL (VIN 3) (p=0.091). For the 12 patients with treatment information available, 8 (67%) received treatment after biopsy (CO2 laser vaporization, imiquimod, cryotherapy, or excision). 1 of 2 p16(+) cases (50%) and 5 of 20 p16(-) cases (25%) had HSIL in additional lower anogenital tract sites (CIN 2-3 or invasive cervical squamous cell carcinoma) (p=0.40).

Conclusions: Flat vulvar LSIL is infrequently p16(+) (7%), suggesting that cell cycle disruption by high-risk HPV infection is uncommon in these lesions. Few patients with vulvar LSIL developed subsequent higher grade vulvar squamous lesions (4.5% of all cases with follow-up), which may be partly due to the frequent use of destructive treatment; however, this rate was higher among p16(+) cases (50%) than p16(-) cases (0%). While this difference was not statistically significant in our study, the findings suggest that p16 positivity in flat vulvar LSIL may have a role in predicting subsequent development of HSIL. Further studies are warranted to better define the significance of this marker in flat vulvar LSIL.
**Title:** Therapies for Cognitive Deficits Associated with Chemotherapy for Breast Cancer: A Systematic Review of Objective Outcomes

**Summary:** At least 20% of women who undergo breast cancer treatment experience cognitive dysfunction during and after treatment. This systematic review summarizes evidence of treatments for these cognitive deficits.

**Objective:** To systematically review evidence of treatments for cognitive deficits associated with chemotherapy for breast cancer in women.

**Methods:**

**Data Sources:** Searches of 5 databases (PubMed, Embase, Cochrane CENTRAL, PsycINFO, CINAHL) with no date or language restrictions identified 1,701 unique results. Search terms included breast cancer, chemotherapy, chemobrain, chemofog, and terms on cognition and language deficits.

**Study Selection:** Included studies: (1) described therapies for cognitive dysfunction in women undergoing (or who had undergone) chemotherapy for breast cancer (2) provided objective measurements of cognition or language, and (3) were published in peer-reviewed journals.

**Data Extraction:** Data were extracted according to Cochrane recommendations including characteristics of participants, interventions, outcomes, and studies. Quality assessment of all 12 eligible studies was performed using PEDro scale and treatment fidelity criteria. Screening, data extraction, and quality assessment reliability was performed.

**Results:** Six articles described interventions for cognition that took place during cancer treatment; six, afterward. Five interventions were medical (including a strength-training program), two were restorative, and five were cognitive. Medicinal treatments were ineffective; restorative and exercise treatments had mixed results; cognitive therapy had success in varying cognitive domains. The domains that were most tested and most successfully treated were verbal memory, attention, and processing speed.

**Conclusions:** Cognitive therapy protocols delivered after chemotherapy and aimed at improving verbal memory, attention, and processing speed hold the most promise. Future research is needed to clarify whether computerized cognitive training can be effective in treating this population and to identify objective assessment tools that are sensitive to this disorder.
**Title:** PERIOPERATIVE DEXAMETHASONE AND THE DEVELOPMENT OF CHRONIC POST-MASTECTOMY PAIN: A SINGLE CENTER OBSERVATIONAL COHORT STUDY

**Summary/Objective:** Perioperative modulation of surgical inflammatory response has been hypothesized as a viable pharmacological preventive target for the development of chronic pain after surgery. The objective of the current investigation was to evaluate an association between intravenous dexamethasone 4-20 mg on the day of surgery with self-reported pain in the breast or axilla at least 3 months after mastectomy.

**Sample:** 310 women that had a unilaterial or bilaterial mastectomy for breast cancer.

**Methods:** The study was a secondary data analysis of a prospective cohort investigation. Subjects who have undergone mastectomy surgery were evaluated at least 3 months after the surgical procedure for the presence of chronic post-surgical pain using validated pain questionnaires. Binary logistic regression analysis was used to determine the odds of development of chronic post-surgical pain in subjects who did and did not receive perioperative dexamethasone.

**Results:** 52 patients (17%) met the IMMPACT criteria for chronic pain in the breast and/or axillary region. 211 out of 310 (68%) subjects received perioperative dexamethasone on doses varying from 4-20 mg. The incidence of chronic pain in the mastectomy group who received perioperative dexamethasone was not different, 15 out 84 (15.2%) compared to 37 out 211 (17.5%) in the group who did not receive perioperative dexamethasone, difference -2% (95% CI -10 to 7, P= 0.75).

**Conclusion:** Perioperative dexamethasone is not associated with a reduction in the incidence and/or severity of chronic post-mastectomy pain. Our results do not support the current concept that short perioperative interventions are effective to prevent chronic postsurgical pain.

**References:**
Title: Association between the administration of intrapartum magnesium and the incidence of intrapartum fever

Summary:
Maternal fever, defined as a temperature ≥ 38° C (100.4° F), is associated with several adverse neonatal outcomes including hypotonia, seizures, and need for resuscitation. An association between the use of intrapartum neuraxial analgesia and maternal fever exists, possibly mediated by interleukin-6. In a murine model, magnesium sulfate suppressed interleukin-6-induced increases in maternal temperature. We hypothesized that patients exposed to intrapartum magnesium would have a lower incidence of fever than patients not exposed to magnesium.

Objective: To evaluate the incidence of maternal fever in relation to administration of intrapartum magnesium therapy.

Methods:
In this retrospective, cross-sectional study, electronic medical record data from all live-born deliveries at Northwestern Memorial Hospital between 2007 and 2014 were evaluated. Cases without temperature data were excluded. Extracted data included parity, gestational age, labor type, membrane status at admission, mode of delivery, the use of neuraxial analgesia/anesthesia, diagnosis of preeclampsia, and whether magnesium sulfate was administered. The primary outcome was the diagnosis of fever. After initial univariable analyses, variables with a P <0.1 were entered into a multivariable model.

Results:
There were 62,646 deliveries that met inclusion criteria; 6,163 of these developed a fever (9.8%). Women who developed fever were more likely to be nulliparous, term, not preeclamptic, have used neuraxial analgesia/anesthesia, and have delivered via cesarean. The incidence of fever was lower in women who were exposed to magnesium than those who were not (4.3% vs. 9.9%, P<0.001). In a multivariable logistic regression model (Table 1), women exposed to magnesium were less likely to develop a fever than those who were not (adjusted odds ratio 0.58, 95% CI 0.42 to 0.81).

Conclusions:
Our data suggest that magnesium may play a protective role against the development of maternal fever. Future work should evaluate the association between the duration of magnesium administration and the development of fever, as well as evaluate neonatal outcomes. These findings should be validated in prospective study, in order to inform the use of magnesium as a potential intervention.
Introduction: Over 800,000 new cases of cancer are diagnosed in women each year. Standard treatments can cause severe thrombocytopenia that may result in heavy menstrual bleeding. The objective of this study was to assess current practices for menstrual suppression and identify the frequency of acute vaginal bleeding that requires gynecologic consultation, medical or surgical intervention, or blood transfusion.

Methods: This was a retrospective case-control study of female patients aged 10-54 with non-gynecologic malignancies treated at Northwestern Memorial Hospital between 2008 and 2013. Women with a documented episode of vaginal bleeding were matched by age, cancer type, and year of diagnosis with women who did not have a bleeding episode. Chi-squared tests estimated differences between groups.

Results: 73 women with an episode of vaginal bleeding were identified and matched with 73 controls. Mean age was 49.4. The most common diagnoses were breast (80.8%) and thyroid cancer (12.3%). Of women with bleeding, 68 required inpatient gynecologic consultation (93.2%) and 36 required intervention (49.3%). The most common interventions were D&C (26%), IUD (9.6%), hysterectomy (6.8%), OCPs (5.5%), and oral progestins (2.7%). One patient received a transfusion. Few patients received menstrual suppressive therapy, but this was more common among women who bled (13.7 vs. 2.7%; p=0.02). Six women used OCPs, 5 an IUD, and 2 a GnRH agonist for suppression.

Conclusions: Among women with non-gynecologic malignancies, treatment-associated thrombocytopenia can result in significant vaginal bleeding, requiring medical or surgical intervention. Optimal preventative strategies should be explored to avoid these complications.
Presenting Author: Alix Leader-Cramer, M.D.
Position: Female Pelvic Medicine and Reconstructive Surgery Fellow
Principle Investigator: Christina Lewicky-Gaupp, M.D.
Department: Obstetrics and Gynecology
Clinical, Basic Science, Public Health, or Social Sciences: Clinical and Women’s Health Research
Email: aleaderc@nmff.org

Title: Timing of Return to Intercourse After Obstetric Anal Sphincter Injuries: Results from the FORCAST Trial (For Optimal Recovery: Care After Severe Tears)

Summary: Postpartum sexual dysfunction in women may be as high as 41-83% in the first 2-3 months postpartum. Although, Masters and Johnson wrote scientifically about the topic in the 1950s, few investigators contributed substantially to our understanding of postpartum sexual dysfunction since that time. More recent studies on whether sustaining obstetric anal sphincter injuries (OASIS) affects timing of return to coitus have been conflicting.

Objective: To determine the proportion of women with OASIS who resume vaginal intercourse within 12-weeks of delivery and identify factors associated with delayed resumption of vaginal intercourse.

Sample: 268 patients who sustained OASIS during vaginal delivery at Prentice Women’s Hospital where included in the original prospective cohort study. 199 of those were included in this secondary analysis, as the remainder were lost to follow-up prior to their 12-week visit.

Methods: We conducted a prospective cohort study of women who sustained OASIS during delivery of a full term singleton infant at a single academic medical institution from September 2011 to April 2014. Demographic and delivery data were obtained from electronic medical records. All patients were seen in the Female Pelvic Medicine and Reconstructive Surgery Clinic at 1, 2, 6, and 12 weeks postpartum, then annually, for perineal examination. Patients completed the Patient Health Questionnaire-9 (PHQ-9), Urinary Distress Inventory-6 (UDI-6), Incontinence Impact Questionnaire-7 (IIQ-7), Visual Analog Scale (VAS) for Pain, and Fecal Incontinence Severity Index (FISI) at every visit. The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire-12 (PISQ-12) was completed at all postpartum visits once resuming vaginal intercourse. We considered vaginal intercourse “delayed” if the patient did not resume intercourse by her 12-week visit. This cutoff was chosen because it was subsequent to the 6 week visit, when patients were instructed to return to normal pelvic activity. Patients were excluded from this analysis if they were lost to follow-up prior to the 12 week visit. SPSS Version 20 was used for statistical analysis. Continuous variables were compared between vaginal intercourse groups using independent samples t-test (normally distributed) or Mann-Whitney U test (not normally distributed). Chi-squared test of association was used for categorical variables.

Results: 199 of 268 (74%) of women enrolled were included in this analysis. 69 women were excluded, as they were lost to follow-up prior to their 12 week visit and had not returned to intercourse by the prior visit. The majority were Caucasian (77%), primiparous (86%), and non-smokers (75%). 80 (40%) women resumed vaginal intercourse before their 12-week visit, while 119 “delayed” return to intercourse. Patients who delayed return to intercourse scored higher on the FISI (more anal incontinence) than those who resumed intercourse by 12-weeks (15.4±12.3 vs. 12.0±12.8, p=0.021). After resumption of intercourse, those who delayed intercourse were more likely to have sexual dysfunction delineated by a higher PISQ-12 score (11.1±5.1 vs. 9.4±4.4, p=0.02). After return to intercourse, the anal incontinence in the “delayed” group persisted compared to the “not-delayed” group, denoted by persistently higher FISI scores (4.0±7.2 vs. 1.6±4.4, p=0.002).

Conclusion: Patients with more severe anal incontinence symptoms after OASIS are less likely to resume vaginal intercourse in the first 12-weeks after delivery. These patients are also more likely to have sexual dysfunction after resuming intercourse in addition to persistence of the anal incontinence symptoms.
**Title:** Type of Hormonal Contraception (HC) and Duration of Use Are Associated with Lower Anti-Mullerian Hormone (AMH) Levels in Young African American Women (AAW)

**Summary:** While a number of studies have suggested HC use results in lower AMH levels, others have found no effect. Few studies have looked at the effect of specific types of HC on AMH level and, to our knowledge, no studies have investigated the effect of long-term HC use on AMH.

**Objective:** Our objective was to determine the impact of type and duration of HC use on AMH level among young AAW.

**Methods:** 1696 women were enrolled in the Study of Environment, Lifestyle & Fibroids (SELF). Eligibility criteria included AA race, age 23-34 years at recruitment, and no history of chemotherapy or radiation for cancer or autoimmune disorders. Blood samples were run on an ultrasensitive AMH ELISA assay (CV<10%). Log AMH was used for the linear regression model, as AMH was not normally distributed.

**Results:** The mean age of the subjects was 28.7±3.5 years (mean±SD). The mean AMH level (ng/mL) was 3.99±3.48. 27.4% of the subjects were currently using some form of HC. Mean AMH level among current HC users (3.31±2.56) was significantly lower than those who had previously used HC (4.25±3.90, p<.001), and those who had never used HC (4.26±3.02, p<.001). Among current HC users, the most commonly used types of HC were oral contraceptive pills (OCPs) (44%), hormonal shot (23%), and levonorgestrel IUD (22%). With the exception of the hormonal patch, all types of HC (OCPs, hormonal implant, vaginal ring, hormonal shot, and levonorgestrel IUD) were associated with significantly lower mean AMH levels, when compared to those not currently using HC. After controlling for age and BMI, OCPs ($\beta$=-.25; SE=.080; p=.002), vaginal ring ($\beta$=-1.15; SE=.21; p<.0001), and hormonal shot ($\beta$=-.37; SE=.011; p=.001) remained associated with lower log AMH values in the multivariate analysis. To further determine the role of duration of HC use on AMH, we restricted our analysis to those subjects who were either currently using HC for at least one month (n=430) or had never used HC (n=233). The mean duration of HC use among current HC users was 75.9±58.2 months (range 1-252 months). When duration of HC use was divided into quartiles, all quartiles of current users had significantly lower AMH levels than never users. When duration of use was considered in tertiles by HC type, lower AMH levels were observed with longer duration of use among subjects using OCPs (T1 [12-96 months] 3.83±2.71, p=.28; T2 [108-132 months] 3.57±2.38, p=.13; T3 [144-252 months] 2.98±3.36, p<.01) and hormonal shots (T1 [1-42 months] 3.57±2.68, p=.20; T2 [48-84 months] 3.47±2.36, p=.14; T3 [93-180 months] 2.36±1.88, p=.001).

**Conclusions:** This study supports an association between current HC use and lower AMH levels, and suggests a differential impact of various types of HC. The mean AMH of previous HC users was not significantly different from those who had never used HC, suggesting that the suppressive effect of HC on AMH is temporary. Further, we found that for OCPs and hormonal shots, increasing duration of use is associated with reductions in AMH levels. Women undergoing ovarian reserve testing should be counseled that AMH levels may be transiently decreased while using HC.
Introduction: Monozygotic twinning has increased with growing use of assisted reproductive technology (ART). Inadequate data examine this phenomenon in triplet pregnancies. We aimed to evaluate trends in the proportions and outcomes of dichorionic-triamniotic (DT) compared to trichorionic-triamniotic (TT) triplet gestations.

Methods: Retrospective cohort of all patients with a triplet gestation identified by first trimester ultrasound (US) and delivered at a large academic center between 2005-14. Chorionicity/amnionicity were determined by US and confirmed on placental pathology. Chi-square, Fisher’s exact and ANOVA tests were used.

Results: 158 triplet pregnancies were identified. 44 (28%) were DT and 113 (72%) were TT. There were no differences in maternal demographic characteristics including age, race, parity or BMI. 152 (96%) conceived by ART. A greater proportion of DT compared to TT triplets conceived by IVF (85% v 59%, p=0.003). There was a significant increase in the proportion of DT pregnancies over time. DT sets were more likely to deliver as a singleton or triplet gestation. While a greater proportion of DT triplets experienced adverse events, these differences did not reach statistical significance (table). There were no differences in maternal outcomes including preeclampsia or hemorrhage (data not shown).

Conclusions: The proportion of triplet gestations that are DT more than doubled from 2005-14 at this institution. Major differences in maternal or neonatal outcomes were not identified. Differences in neonatal morbidity may be apparent in a larger sample size.

Table: Perinatal outcomes for dichorionic and trichorionic triplet gestations

<table>
<thead>
<tr>
<th></th>
<th>Dichorionic-Triamniotic N (%)</th>
<th>Trichorionic-Triamniotic N (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time period*</td>
<td>N=45</td>
<td>N=113</td>
<td></td>
</tr>
<tr>
<td>2005-07 (n=37)</td>
<td>6 (16)</td>
<td>31 (84)</td>
<td>0.003</td>
</tr>
<tr>
<td>2008-10 (n=54)</td>
<td>13 (24)</td>
<td>41 (76)</td>
<td></td>
</tr>
<tr>
<td>2011-14** (n=67)</td>
<td>26 (39)</td>
<td>41 (61)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous fetal reduction (n=23)</td>
<td>4 (8.9)</td>
<td>19 (16.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Selective fetal reduction (n=64)</td>
<td>17 (37.8)</td>
<td>47 (41.6)</td>
<td>0.66</td>
</tr>
<tr>
<td># of fetuses at delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One (n=28)</td>
<td>16 (35.6)</td>
<td>12 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Two (n=55)</td>
<td>4 (8.9)</td>
<td>51 (45.1)</td>
<td></td>
</tr>
<tr>
<td>Three (n=75)</td>
<td>25 (55.6)</td>
<td>50 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Neonatal death (n=9)</td>
<td>5 (11.1)</td>
<td>4 (3.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Delivery &lt;24 weeks (n=8)</td>
<td>4 (8.9)</td>
<td>4 (3.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Delivery &lt;30 weeks (n=12)</td>
<td>8 (17.8)</td>
<td>11 (9.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Intrauterine growth restriction &lt;10th percentile (n=12)</td>
<td>4 (8.9)</td>
<td>15 (13.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Twin-twin transfusion syndrome (n=3)</td>
<td>3 (6.7)</td>
<td>0 (0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Percent of triplets in that time period **2014 data to date
Title: The frequency of and factors associated with adverse events on Labor & Delivery

Objective: To estimate the frequency of adverse events on a labor and delivery unit and discern whether there are particular patient factors that predict their occurrence.

Sample: All women admitted to Prentice Labor & Delivery during rotating 8-hour periods each day over a 6-week period.

Methods: This was a prospective cohort study of the labor & delivery unit at Prentice Women’s Hospital. A trained observer was present on the unit to monitor for the occurrence of predefined trigger events that served to signal the increased likelihood of a quality problem (defined as an adverse event or potential adverse event). A three person multi-disciplinary team evaluated each trigger event and determined by consensus not only whether it was an adverse event or potential adverse event, but also the event’s preventability or potential to cause harm, respectively. An example of an adverse event is an intra-operative injury and an example of a potential adverse event is a delay in drug delivery. The frequency of adverse events and potential adverse events was determined and their association with patient factors estimated.

Results: The study included 213 patients admitted to L&D. Twenty-eight patients (13%) were determined by the multidisciplinary team to have had an adverse event and 18 (8%) were classified as experiencing a potential adverse event. Most adverse events (N = 23) were judged to be related to the patients’ underlying conditions or natural progression of disease, although 5 events (i.e., 17% of adverse events) were judged to be related to healthcare management and to have been preventable. Of potential adverse events, 51% were judged to have the potential to cause harm. No patient factors (Table) were found to be associated with adverse or potential adverse events (P > .05 for all).

Conclusion: Adverse events or potential adverse events occurred in approximately 1 in 5 women admitted to a labor and delivery unit. No factors were found that identified which women were more likely to experience a quality problem.
Title: Trends in Income, Race and Ethnicity Disparities in Guidelines for Breast Conserving Therapy

Summary/Objective: NCCN guidelines for treatment of breast cancer recommend treatment with breast-conserving therapy (BCT) for early stage breast cancer, without positive margins (PM), whole breast radiotherapy (RT), chemotherapy and hormonal therapy when appropriate. We analyzed trends in guideline adherence by income, education, race and ethnicity from the National Cancer Data Base (NCDB) 1998-2011.

Sample/Methods: Women with stage I and stage II breast cancer (T1N0 or T1N1, n=492,333) were identified from 1123 hospitals. Logistic regression was used to study the proportion of eligible patients receiving BCT, their margin status after surgery, and adherence to NCCN treatment guidelines for radiation, hormone and chemo therapy. Analyses of the effects of race and ethnicity, income and education and insurance status were controlled for age, type and region of hospital.

Results: BCT disparities remained similar for non-Hispanic whites (79.9-87.3%), Blacks (80.0-85.7%) and Hispanics (79.1-85.2%) and increased between the highest versus lowest zipcode income and education quartiles. Among BCT patients, PM disparities between non-Hispanic whites (7.6-3.7%), and Blacks (9.3-4.5%) and Hispanics (11.6-4.6%) and across income and education quartiles improved. No RT disparities improved for Blacks (24.7-20.5%) and Hispanics (27.0-22.0%) but not between income and education quartiles. Regression results for all years indicated that white-Black BCT differences were non-significant, but Hispanics had 13% lower likelihood of BCT; highest and lowest income quartiles differed by 5-7%. PM were higher for Blacks and Hispanics (16%, 8%) but did not differ by income and education. Hispanics and low income patients were less likely to receive RT while Blacks were more likely and education differences were non-significant. Older women, >70 were less likely to receive hormonal and chemotherapy.

Conclusion There was a mixed pattern of progress in reducing guideline disparities. Other risk factors such as older age, insurance status, region and hospital type were more significant than zipcode socioeconomic status, race and ethnicity. These results are conservative to the extent that the NCDB reflects higher quality of care than non-participating hospitals.
Presenting Author: Paul C. Fitzgerald, RN  
Position: Clinical Research Nurse  
Principal Investigator: Jeanette Bauchat, MD  
Department: Anesthesiology  
Clinical, or Basic Science, or Public Health and Social Sciences: Clinical / Women's Health Research  
Email: p-fitzgerald2@northwestern.edu

Title: Developing a Standardized Checklist for Labor and Delivery Multidisciplinary Rounds Using the Delphi Method

Intro: Communication failures among healthcare providers contribute to up to 85% of sentinel events. The use of checklists and cognitive aids during multidisciplinary rounds can facilitate team understanding and coordination of patient care. Obstetric, anesthesiology, and nursing teams convene twice-daily for multidisciplinary rounds at the Prentice Women’s Hospital labor and delivery suite, but these rounds lack structure. The purpose of this study was to develop a standardized checklist to inform the content of these rounds.

Methods: A Delphi technique was used to achieve a consensus among a multidisciplinary group of experts (4 obstetricians, 4 anesthesiologists, and 4 nurses) on what content should be addressed during multidisciplinary rounds. A preliminary list of 36 items was generated by the investigators. The experts were asked to rank each item according to importance on a five-point Likert scale (1- not important to 5- very important). In the 2nd round, experts were shown each item’s mean rating by all experts, their own original rating of that item, and additional suggestions by experts, and were given the opportunity to update their responses. Consensus was reached after two Delphi rounds. A final checklist was developed incorporating items with a mean importance >3 and a coefficient of variance (Cv) <0.5. Experts then rated the importance of each item on the final checklist. At each stage experts could suggest wording, theme modifications, or item inclusions.

Results: In the 1st round, mean importance rating was 3.49, with 13 of 36 items rated ≥4 with Cronbach’s α=0.77. In the 2nd round, the mean importance rating was 3.42, 12 items were rated ≥4, and 14 items rated between 3 and 4 with Cronbach’s α=0.92. No additional item suggestions were rated highly enough for inclusion. The final checklist incorporated all items rated >3 with a Cv <0.5. The mean importance of all final checklist items was 4.4 (±0.4) with a Cv 0.1 (± 0.2) and Cronbach’s α= 0.827.

Discussion: Delphi methodology was used to develop a standardized checklist for implementation on labor and delivery multidisciplinary rounds. Future studies will investigate utilization and patient outcomes following implementation of this standardized format.

Weighing in on Reproductive Health: The Impact of Obesity on Antimüllerian Hormone (AMH) in Young African American Women (AAW)

Objective: Obesity is a growing epidemic with concerning implications for women's reproductive health. Although some studies have reported that obesity may specifically be associated with decreased ovarian reserve, others have failed to demonstrate such a relationship. The objective of this study is to determine whether there is an association between body mass index (BMI) and AMH levels in young AAW.

Methods: This cross-sectional study included 1,645 AAW aged 23-35 years who participated in the Study of Environment, Lifestyle & Fibroids (SELF). An ultrasensitive ELISA assay was used to determine AMH. Log-transformed AMH was used as the outcome in both simple and multiple linear regression models. A simple linear regression model was used to assess its relationship with each covariate. To further investigate its relationship with BMI, while controlling for age and current use of hormonal contraception, a multiple linear regression model was used.

Results: The mean subject age was 28.7±3.5 years (mean±SD) and the mean AMH was 4.00±3.49 ng/mL (range <.002-39.4). The mean BMI was 33.6±9.4 kg/m2 (range 15.9-79.4), with 59.5% of the subjects being obese (BMI≥30). There was a significant inverse relationship between AMH and BMI (β=-.012;SE=.003;P<.0001), and the association remained after adjusting for age and current use of hormonal contraception (β=-.012;SE=.003;P<.0001). There were also significant inverse relationships between AMH and self-reported weight at age 18 (β=-.002;SE=.001;P=.002), heaviest reported lifetime weight (β= -.002;SE=.0004;<.0001), and age at maximum weight (β=.030;SE=.006;P<.0001). There was no significant association between AMH and a history of weight cycling.

Conclusions: The findings from this large study of young AAW suggest that obesity negatively impacts ovarian reserve, as current BMI, weight at age 18, maximum lifetime weight, and age at maximum weight were all inversely associated with AMH. Given high obesity rates in AAW, it is imperative that the reproductive sequelae of obesity are better characterized and addressed in this group of women.
Presenting Author: Bhumy Dave, MD
Position: Female Pelvic Medicine & Reconstructive Surgery Fellow
Principal Investigator: Kim Kenton, MD, MS
Department: Obstetrics and Gynecology
Clinical, or Basic Science, or Public Health and Social Sciences: Clinical and Women’s Health Research
Email: bdave@nmff.org

Title: Effect of Anesthesia Type on Perioperative Outcomes for Midurethral Sling

Objective: To determine if there is a difference between intra- and perioperative outcomes for patients undergoing midurethral sling (MUS) placement under general anesthesia (GA) as compared to monitored anesthesia care (MAC)

Sample: A cohort of 225 women undergoing outpatient placement of synthetic retropubic midurethral sling

Methods: We performed a retrospective analysis on women undergoing outpatient placement of synthetic retropubic midurethral sling under general anesthesia (n=141) or monitored anesthesia care (n=84) between 2009 and 2014. Patients undergoing concomitant procedures were excluded. Exposure variable was type of anesthesia. Primary outcomes were operative, surgical, and recovery times. Secondary outcomes included cost, discharge home with a catheter, and postoperative pain or nausea.

Results: In the general anesthesia group, both operating room time (mean ± SD, 67.6 ± 13.3 min vs. 56.9 ± 11.8 min, p<.001) and recovery room time (240.0 ± 69.8 min vs. 190.1 ± 78.3 min, p<.001) were longer, whereas there was no difference in actual surgical time (30.0 ± 8.9 min vs. 29.0 ± 9.7 min, p=.436) between anesthesia groups. Cost was significantly higher in the general anesthesia group ($4095 ± 715 vs. $3877 ± 777, p=.030). No major intraoperative complications were identified in either group. There was no difference in rates of bladder perforation (6.4% vs. 11.9%, p=.337) between the groups. Patients with general anesthesia had higher rates of discharge with a catheter (27% vs. 16%, p=.045) and higher pain scores as measured by verbal rating scale (Median 1.7, IQR 0.56, 3.00 vs. 0.94, IQR .00, 2.45, p=.006) than those with monitored anesthesia care; there was no difference in antiemetic use in the recovery room (12.1% vs. 9.5%, p=.791).

Conclusion: Monitored anesthesia care may offer significant benefits over general anesthesia in women undergoing retropubic midurethral sling, including shorter operating room and recovery times, lower cost, less postoperative pain, and less voiding dysfunction in the immediate postoperative period with no increase in complications.
Duration of Catheterization after Retropubic Midurethral Sling Surgery

Summary: The midurethral sling has become the gold-standard surgical treatment for female stress urinary incontinence. Temporary postoperative urinary retention is a known complication, effecting approximately 1 in 4 women undergoing the procedure. Urinary retention following this common procedure is considered temporary, but the actual duration is not known.

Objective: To describe the duration of urinary retention requiring catheterization in women discharged performing intermittent self-catheterization (ISC) on the day of retropubic midurethral sling (MUS) surgery.

Methods: We conducted a retrospective cohort analysis of women who underwent outpatient retropubic MUS surgery between January 2009 and July 2014. All procedures were performed by fellowship-trained Female Pelvic Medicine & Reconstructive Surgeons. Demographic, intraoperative, and postoperative data were obtained from the electronic medical record. Patients who had concomitant procedures, incomplete voiding trial (VT) data, or incomplete postoperative catheterization data were excluded. A standard retrograde-fill voiding trial was performed on all patients on the day of surgery prior to discharge. Those who did not pass their VT were included in the analysis. Subjects were categorized into one of two groups: “mild” retention, defined as having a post void residual (PVR) >1/3 and < 2/3 the total bladder volume, and “severe” retention, defined as having a PVR ≥ 2/3 the total bladder volume. Patients were instructed to discontinue catheterization after achieving two consecutive PVR volumes of <75ml; duration of postoperative catheterization was determined in days. Continuous variables were compared between groups using the Mann-Whitney U test, and Spearman’s Rho correlation was used to measure the strength of association between continuous variables.

Results: Of the 200 patients who underwent MUS surgery in the study time period, 47 (23.5%) did not pass their postoperative VT on the day of surgery. Four patients had incomplete postoperative catheterization data, leaving 43 patients for final analysis. Subjects had a mean ± SD age of 49 ± 11 years. The majority were Caucasian (69%) and parous (90%). The median (IQR) PVR volume postoperatively for the cohort was 250ml (190, 325). Thirty-nine patients (90.7%) in the cohort were able to perform intermittent self-catheterization (ISC). Median days of postoperative catheterization for the cohort were 2.00 (1.00, 4.00). Thirty-seven percent catheterized for 1 day, 32.5% for 2 days, 2.5% for 3 days, and 27.5% for >3 days. Seventeen (39.5%) met criteria for “mild” retention and 26 (60.5%) met criteria for “severe” retention. There was no difference in the number of days of postoperative catheterization between the “mild” and “severe” retention groups (median 1, IQR 1.00, 2.75 vs. median 2, IQR 1.25, 4.00, p=0.156). Neither time spent in the recovery room nor average pain scores, as measured on a standard postoperative verbal rating scale, were associated with days of catheterization or PVR volumes.

Conclusions: Our study found that the majority of women discharged performing ISC after retropubic MUS will void adequately within 1-2 days with few requiring ISC after 2 days. In addition, our data demonstrated a trend suggesting that women with more severe immediate postoperative urinary retention may require catheterization for a longer duration. These data will be helpful when counseling patients regarding length of catheterization after MUS surgery; allowing patients to formulate realistic expectations and potentially alleviate anxiety regarding postoperative catheterization.
The natural history of peri-operative overactive bladder symptoms among women undergoing midurethral sling surgery

Midurethral slings are the most widely performed surgeries for stress urinary incontinence (SUI), with over one million procedures completed to date\(^1,2\). Surgical satisfaction is strongly related to surgical efficacy and post-operative symptoms of overactive bladder (OAB) with the cardinal symptom of urgency, often accompanied by frequency and/or urgency incontinence\(^1,3\) (UUI). Women with more severe pre-operative OAB symptoms are at greatest risk for post-operative bothersome OAB symptoms\(^3\)\(^-\)\(^5\). Yet, the natural history - the timing and potential resolution of these symptoms - remain poorly understood.

**Objective:** To describe the natural history of peri-operative OAB symptoms using validated questionnaires.

**Sample:** Women undergoing synthetic retropubic midurethral sling (MUS) at Prentice Women’s Hospital by a board certified urogynecologist.

**Methods:** Consecutive women undergoing MUS without concomitant procedures were invited to participate in this prospective longitudinal cohort study characterizing pre- and postoperative urinary symptoms. Urinary symptoms were assessed using two symptom questionnaires: Urinary Distress Inventory (UDI-6) and Overactive Bladder Questionnaire (OAB-q) at baseline (before MUS) and 2, 6, 12 and 13 weeks after surgery. OAB symptoms were separated into two clusters for analysis: (1) Frequency and (2) Urgency Incontinence (UUI).

**Results:** The data of 36 women were analyzed. Out of the 17 subjects without preoperative frequency symptoms, 10 reported frequency 2 weeks postoperatively (59%), and 7 reported frequency 6 weeks postoperatively (41%). By week 13, only 3 of these subjects continued to experience frequency symptoms (18%). Out of the 19 patients that endorsed frequency preoperatively, 12 continued to experience frequency 2 weeks postoperatively (63%), and 10 experienced frequency after 6 weeks (53%). By week 13, 10 of these subjects continued to experience frequency postoperatively. Out of the 15 patients without preoperative UUI, 6 patients endorsed UUI 2 weeks postoperatively (40%), 3 endorsed UI after 6 weeks (20%), and only 1 patient endorsed UUI at 13 weeks postop (<1%). Out of the 21 patients that endorsed preoperative UUI, 6 continued to endorse UUI at their 2 week POV (29%), 7 endorsed it at their 6-week POV (33%), and 11 endorsed UI at their 13 week POV (52%).

**Conclusions:** Over half of women undergoing MUS develop OAB symptoms immediately after surgery, but most OAB symptoms resolve by 13 weeks after surgery. Persistent de novo OAB or UUI is rare. In contrast, symptoms are more likely to persist in patients with preoperative OAB. These data may provide useful information for patient guidance and counseling. Future studies are necessary to determine the etiology for transient OAB symptoms after surgery.

Presenting Author: Kelly L. Stempinski, MPH
Position: Adjunct Associate Professor
Principal Investigator: Elizabeth Feldman, MD, FAAFP, CCHP
Department: Family and Community Medicine, Feinberg School of Medicine
Clinical, or Basic Science, or Public Health and Social Sciences: Clinical and Women’s Health Research
Email: efeldman@cookcountyhhs.org

Title: Reproductive Health in Newly Incarcerated Women within a County Jail

Kelly Stempinski1, Alicia Roston1, Erica O'Neill1,2, Elizabeth Feldman3, Kathleen Talamayan3, Linda Forst4, Ashlesha Patel1,2
1Department of Obstetrics and Gynecology, John H. Stroger Hospital of Cook County, Chicago, IL, USA, 2Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, 3Cermak Health Services, Cook County Health and Hospitals System, Chicago, IL, USA, 4Department of Environmental and Occupational Health Sciences, School of Public Health, University of Illinois at Chicago, Chicago, IL, USA

Objective: To assess the risk of unintended pregnancy among women at a county jail intake. We will assess the interest in and need for immediate emergency contraceptive administration, as well as future contraceptive desire.

Methods: We performed a cross-sectional in-person survey at the time of Cook County Jail intake. Study participants included women 18-50 years of age who consented to the study. The interviews were performed on selected evenings from June 2011 to August 2012. Study questions were multiple-choice close-ended questions. Topics focused on included current pregnancy risk, current pregnancy desire, previous contraceptive use, and desire for future contraceptive use.

Results: A total of 194 women completed the survey. Excluding women not at risk for pregnancy (5% currently pregnant, 20% surgically sterilized/postmenopausal, and 5% using long-acting reversible contraceptives), 78% of women who were at risk for pregnancy (n=137) did not desire pregnancy. Among these women at risk for unintended pregnancy, 9 (7.5%) had unprotected intercourse within 5 days prior to survey administration. When asked about emergency contraception, most women would be interested if available. Eighty percent of women would be interested in contraceptive supplies if provided free at release from jail.

Conclusions: Reproductive age women presenting to county jail are at significant risk for unintended pregnancy and could benefit from availability of emergency contraception at intake and contraceptives at release.
Title: The utility of ultrasound in predicting SGA in pregnancies complicated by isolated single umbilical artery

Objective: To assess the association of isolated single umbilical artery (iSUA) with small for gestational age (SGA) neonates and preterm birth (PTB) as well as evaluate the utility of ultrasound in detecting fetal growth restriction.

Methods: In this retrospective cohort study, 219 consecutive women with pregnancies complicated by iSUA were compared with 219 women with a 3-vessel cord. Pregnancies with fetal anomalies or aneuploidy were excluded from the analysis. Univariable comparisons of patients’ characteristics and pregnancy outcomes were conducted using chi-square test or Fischer exact test for categorical data, and student t-test for continuous measures. Multivariable linear regression was performed to assess the association between iSUA, gestational age at delivery and birth weight, and logistic regression was done to determine whether the presence of iSUA was associated with SGA or PTB.

Results: In univariable analysis, the presence of iSUA was significantly associated with lower birthweight and with SGA (p<0.001 for each outcome). Earlier gestational age at delivery as well as delivery < 34 and < 37 weeks also were more common in pregnancies with iSUA (p=0.003 for both). However, no significant difference was noted between estimated fetal weights in the iSUA group compared to the control group, as measured on growth ultrasounds at either 28-32 weeks (57.2% vs 57.1%, p=0.939) or 34-38 weeks (60.0% vs 65.1%, p=0.178). In multivariable analysis, iSUA remained associated with SGA and PTB <37 and <34 weeks (aOR=3.97, CI 1.55-10.12, aOR=2.69, CI 1.30-5.56, aOR=10.91, CI 1.36- 87.65, respectively).

Conclusion: Pregnancies complicated by iSUA are at increased risk for SGA and preterm birth. However, it appears that antenatal ultrasounds were not able to reliably detect growth restriction in those fetuses.

Key words: growth restriction, preterm birth, single umbilical artery, two vessel cord, ultrasound
Title: A Prospective Study of Depression and Anxiety Among Fertility Preservation and IVF Patients

Angela K. Lawson¹, Susan C. Klock¹, Mary Ellen Pavone¹, Jennifer Hirshfeld-Cytron², Kristin N. Smith¹, and Ralph R. Kazer¹. ¹Northwestern University, 675 North St. Clair Street, Suite 14-200, Chicago, IL, 60611 and ²University of Illinois-Chicago, 820 S. Wood Street, M/C 808 Chicago, IL, 60612.

Summary: Young cancer patients are increasingly interested in preserving their fertility prior to undergoing gonadotoxic therapies. Although the medical safety and treatment protocols for fertility preservation (FP) in women via controlled ovarian hyperstimulation (COH) have been well documented, there is limited research addressing the psychological issues that arise in female FP patients.

Objective: To prospectively assess anxiety, depression, coping, and appraisal in female fertility preservation patients compared to infertile patients.

Sample: 40 patients (19-39y; ̅x = 31.9y) with cancer and 80 age-matched vitro fertilization (IVF) controls (26-36; ̅x = 31.4y) who underwent fertility preservation or IVF.

Method: Patients completed a pre and post-treatment survey including demographics; depression (CES-D), anxiety (STAI), Ways of Coping (WOC), infertility–related stress (FPI), appraisal of treatment (ALE), and treatment expectations.

Results: FP patients reported greater state and trait anxiety than IVF patients, but IVF patients’ anxiety worsened over time. 37% of FP and 11% of IVF patients’ scores exceeded the clinical cut-off for depression on the CES-D at pre-treatment (p < .001). IVF patients were more optimistic about treatment, despite experiencing more loss related to infertility than FP patients (p < .05). 44% of FP and 18% of IVF women thought they had > 60% chance of pregnancy despite being given lower case specific pregnancy rates. Coping strategies and infertility-related stress did not differ between groups. Insurance covered most treatment expenses for 69% of IVF patients and 38% of FP patients (p <.01).

Conclusions: FP patients reported more anxiety and depression than infertile patients at enrollment in treatment, with more than one third of FP patients reporting clinically significant depressive symptoms. However, infertile patients’ anxiety and depressive symptoms increased across treatment. This increase was not related to time between registration for IVF and oocyte retrieval or the medical aspects of treatment. FP and infertile patients should be provided psychological consultation prior to treatment to identify mood and anxiety symptoms and to refer patients for counseling as needed to prevent worsening of symptoms.
Title: Utilization of the Family Planning Quotient in Three Cohorts of Women

Lindsay Zimmerman, MPH\textsuperscript{a}, Kelly Stempinski, MPH\textsuperscript{a}, Aisha Fatima, MBBS\textsuperscript{a}, Vanessa Cullins, MD, MPH, MBA\textsuperscript{b}, Ashlesha Patel, MD, MPH\textsuperscript{a,c}
\textsuperscript{a}Division of Family Planning, Department of Obstetrics and Gynecology, John H Stroger Jr., Hospital of Cook County, Chicago, IL 60612
\textsuperscript{b}Planned Parenthood Federation of America, New York, NY 10001
\textsuperscript{c}Feinberg School of Medicine, Northwestern University, Chicago, IL 60611

Summary: In response to CDC’s reproductive life plan, we developed the Reproductive Life Index (RepLI), and its unit of measure, the Family Planning Quotient (FPQ), to visually present and quantitatively assess reproductive health goals and outcomes.

Objective: The objective of this study is to present utilization of FPQ in three populations.

Methods: FPQ is a ratio of the number of children a woman has divided by the number she wants, at one time point. FPQ less than 1 indicates a woman wants more children and FPQ greater than 1 indicates a woman has achieved or exceeded her family plans. FPQ can be used on a population level to capture overall reproductive health status. FPQ was sampled in three populations: 468 family planning providers (FPP) in a national survey of family planning providers, 1,780 patients presenting for first-trimester abortion (FAP), and 124 patients in the Title X program (TXP).

Results: Among FPP, 59.2% had a quotient less than 1, 39.3% equal to 1, and 1.5% greater than 1. Among FAP, 35.9% had a quotient less than 1, 58.9% equal to 1, and 5.2% greater than 1. Among TXP, 44.4% had a quotient less than 1, 49.2% equal to 1, and 6.5% greater than 1. FPQ were significantly different when stratified by age among the FPP (p<0.001), FAP (p<0.001), and TXP (p=0.004).

Conclusions: RepLI/FPQ is an innovative tool to assist patients and providers in the discussion of reproductive health plans and should be further implemented to demonstrate its impact on reproductive planning.
**Presenting Author:** Lindsey C. Karavites, MD  
**Position:** Visiting Postdoctoral Research Fellow  
**Principal Investigators:** Seema A. Khan, MD and Karen Kaiser, PhD  
**Departments:** Surgery and Medical Social Sciences  
**Category:** Public Health and Social Sciences  
**Email:** Lindsey.karavites@northwestern.edu  
**Title:** Awareness and Acceptability of Skin Application of Preventive Medications for Breast Cancer

**Summary:** Despite multiple trials demonstrating the efficacy of selective estrogen receptor modulators for breast cancer risk reduction, acceptance of these medications remains low due to their multiple known adverse systemic effects. A novel delivery method of local transdermal therapy should significantly reduce these systemic effects thereby increasing acceptance. Women were interviewed and the majority stated that they would prefer the skin application to the conventional oral route of delivery.

**Objective:** To better understand women’s knowledge and perceptions of breast cancer prevention medications and determine if a topical administration of these medications would increase acceptability.

**Sample:** Four focus groups (N=32) were conducted.

**Methods:** Focus groups were conducted with high and standard risk women identified through the Bluhm Family Program for Breast Cancer Early Detection and Prevention at the Robert H. Lurie Comprehensive Cancer Center. An experienced focus group moderator led participants through a discussion of breast cancer risk perceptions, knowledge of and concerns about risk reduction medications, and views of a skin application of risk reduction medication. Participants also provided sociodemographic information, breast cancer risk factors, and prior physician recommendations to take medication to reduce breast cancer risk. Trained research personnel examined all qualitative results systematically. Participants’ breast cancer risk was estimated using the Gail Model.

**Results:** Most participants had at least a college degree (78.2%) and were of either Eastern European (50%) or African ancestry (31%). The majority of the sample (72%) was at elevated risk for breast cancer, just over half of these women perceived themselves to be at higher than average risk. Nineteen percent of participants had prior knowledge of preventive medications. Women who perceived themselves to be at high risk for breast cancer were more likely to know about preventive medications than those who did not perceive themselves to be at elevated risk, 38% vs 0% respectively. Over 90% of the focus group participants stated that they would prefer a topical application of a preventive medication to a pill if their physician advised them to take preventive medication. Concerns about topical medications included the impact on day-to-day life, dosage, medication characteristics, side effects, and possible dangers to others.

**Conclusions:** Awareness of preventive medications was low even in a highly educated sample of high-risk women. If given a choice in the route of administration of chemoprevention, nine out of ten women preferred a gel skin application to an oral pill. Future work should focus on establishing the side effect reduction of topical 4-OHT over oral tamoxifen and raising awareness of chemopreventive medications for breast cancer to increase acceptance of preventive medications, reduce breast cancer incidence, and save lives.

**Acknowledgments:** The Lynn Sage Cancer Research Foundation; Northwestern University Department of Surgery and Department of Medical Social Sciences; UIC/Mt Sinai Hospital Department of Surgery
**Title:** Anesthesiologist trainees’ perceived barriers to providing empathetic care for women undergoing unscheduled cesarean deliveries

**Summary:** Patient satisfaction, a key patient-centered outcome, is critical to improving health outcomes. In systematic reviews, the most important factor influencing maternal satisfaction and birth experience was, “the attitudes and behaviors of the caregivers.” Emergency cesarean delivery can lead to emotional distress, postpartum depression, and post-traumatic stress disorder, particularly in mothers who did not feel supported by their healthcare professionals. Empathy declines throughout medical training. In academic centers, the anesthesiologist trainee is the primary physician interacting with women during unscheduled cesarean delivery (UCD) potentially influencing maternal satisfaction and postpartum well-being.

**Objective:** This is a qualitative exploratory study to elicit anesthesiologist trainees’ perceived barriers to providing empathetic care during UCD.

**Sample:** Interviews (N=10 trainees) continued until saturation of themes was achieved.

**Methods:** This is part of an IRB-approved study. Resident and fellow anesthesiologists were recruited via email, consented and compensated to participate. They were individually interviewed regarding their approach to communicating with women during UCD. Semi-structured interviews consisting of nine questions lasted approximately 15 minutes. Interviews were conducted by a qualitative researcher who was not a physician or a resident supervisor. Interviews were audiotaped and transcribed. Two researchers independently reviewed the interviews for themes. Individual codes were then compiled into one document and the two coders met and discussed inconsistencies to identify the emergent themes.

**Results:** Trainees’ typical approach to caring for mothers involves completing medical tasks and providing factual information. Communicating with the mother beyond factual information is viewed as “optional” to clinical care. Primary barriers that residents perceived in providing empathetic care in urgent cases include managing their own affect and completing medical tasks quickly, which they prioritize over communication. Trainees felt they should provide “reassurance without commitment” and wanted to learn “best practice phrases”. They feel they learn communication skills through role models but no resident could verbalize or model empathetic phrases when asked. They believe nonverbal support (i.e. physical touch) should be based on resident comfort level.

**Conclusions:** Anesthesiologist trainees perceive communication and empathetic care as separate and less important when providing medical care to women particularly in urgent situations. Resident empathy curriculums should address these issues to provide residents with strategies to maximize their interpersonal interactions with women undergoing UCD in an effort to improve women’s postpartum emotional states.
Title: Are We Failing to Treat? Trends in the Omission of XRT after Lumpectomy for Breast Cancer in the United States

Summary: Post-lumpectomy radiation therapy (XRT) has been the standard of care for the treatment of ductal carcinoma in situ (DCIS) and breast cancer. There may, however, be a growing trend towards the omission of radiation therapy given recent studies that suggest that XRT may be omitted in specific populations without a survival disadvantage.

Objective: Our objective was to examine trends in adjuvant XRT use in patients undergoing lumpectomy for DCIS or invasive breast cancer.

Sample: Patients in the NCDB with stage 0-III breast cancer who received lumpectomies between 1998 and 2011 were included. Patients treated at hospitals that were not continuously present in the NCDB from 1998-2011 were excluded, as well as those with Stage IV disease.

Methods: From the National Cancer Data Base (NCDB), 540,040 lumpectomies at 1123 hospitals were identified from 1998-2011. Changes in XRT use over time were explored using random effects logistic regression analyses, adjusting for patient demographics, tumor characteristics, and hospital type.

Results: XRT was used in 61.6% of patients with DCIS and 80% of patients with invasive cancer. The proportion of patients receiving XRT in both groups increased from 1998-2011 (DCIS: 57.1% to 64.4%; invasive: 78.0% to 80.8%; P<0.001 for both). However, in adjusted analyses, lumpectomy patients treated in 2010-2011 were less likely to receive XRT than those treated in 1998-2000 (DCIS: OR 0.87, 95% CI 0.83 to 0.91; invasive: OR 0.92, 95% CI 0.89 to 0.94; P<0.001). Compared to 1998-2000, in 2010-2011, the elderly were less likely to receive XRT (DCIS: OR 0.91, 95% CI 0.84 to 0.99; invasive: OR 0.69, 95% CI 0.66 to 0.72; P<0.001) as were patients<40 with DCIS (OR 0.57, 95% CI 0.41 to 0.80). Although a greater proportion of patients received XRT in 2010-2011 than in 1998-2000, changes in hormonal therapy use and tumor grade distribution over the study period resulted in a lower likelihood of XRT in 2010-2011 in adjusted analyses. After the 2002 approval of the MammoSite device, the proportion of patients receiving accelerated partial breast irradiation increased significantly (DCIS: 0.6% to 6.1%, P<0.001; invasive: 1.3% to 7.4%, P<0.001).

Conclusions: When adjusted for covariates, the likelihood of patients with stage 0-III breast cancer to receive post-lumpectomy XRT decreased from 1998-2011. Omission of XRT may be reasonable in selected populations, but this trend is concerning and could reflect inappropriate extrapolation of studies supporting selective XRT omission. The reasons for the continued omission of guideline-recommended XRT merit further investigation.
Title: Postpartum contraceptive choice among patients after high-risk pregnancy

Objective: Half of pregnancies in the United States are unintended. We hypothesized that a high-risk pregnancy might represent a “teachable moment” regarding contraceptive options.

Methods: This was a retrospective study of women delivering at a university hospital during 2009-2010 who received prenatal care in the faculty or resident clinics. High-risk status was defined by SMFM guidelines; categorizations were agreed upon by all authors. Contraceptive plan and actual methods used were abstracted from clinic and hospital records. Subsequent pregnancies identified through March 2013 were identified. Chi-squared tests assessed correlations between risk status and both contraceptive choice and subsequent pregnancy. Binary logistic regression was performed for the outcomes of Tier 1 contraceptive choice at last contact and for subsequent pregnancy during the follow up period.

Results: 3063 women were included, 2048 low-risk and 1015 high-risk. The index pregnancy was slightly more likely to be unintended among low-risk than high-risk women (48.4% vs. 42.9%, p=0.02). When contraceptive methods were categorized according to WHO tiers, intention to use Tier 1 (most effective) contraceptives was high for both groups antepartum (54.4% low-risk vs. 58.0% high-risk, p=0.202), slightly decreased at hospital discharge (42.3% vs. 50.7%, p<0.001) and significantly decreased postpartum (33.8% vs. 40.1%, p=0.002). Actual use was low for both groups, with just 776 women receiving a Tier 1 method during the study period (25.3%). During follow-up, 656 women (21.4%) had a second pregnancy lasting more than 20 weeks. These were unintended among 36.6% of low-risk and 32.4% of high-risk women, which was not statistically different.

Conclusions: Women experiencing high-risk pregnancy were no more likely to have planned their index pregnancy. While their uptake of highly effective contraception was slightly higher postpartum, they were as likely to have an unplanned pregnancy during follow up. New strategies are needed to counsel all women about pregnancy planning and contraception.
Title: Rates of preterm birth (< 37 weeks, PTB) and small for gestational age (weight for gestational age < 10th percentile, SGA) among African-American and non-Latino White twins: the effect of maternal birth weight.

SUMMARY. Maternal low birth weight (< 2500g, LBW) is well known risk factor for adverse singleton birth outcomes, including rates of PTB and SGA. Exploratory data shows that former LBW (compared to non-LBW) African American mothers have a greater LBW rate among twins.

OBJECTIVE. To determine the extent to which maternal LBW is a risk factor for PTB and SGA among African-American and non-Latino White twins.


RESULTS. In Illinois, former LBW African-American mothers (n=103) had a greater PTB rate among twins than former non-LBW African-American mothers: 67% vs. 55%, respectively; RR = 1.3 (1.1-1.4). There were minimal significant differences in the distribution of demographic, medical, and behavioral characteristics between former LBW and non-LBW African-American mothers. In a multivariate binomial regression analysis, the adjusted (controlling for maternal age, education, marital status, parity, prenatal care usage, and cigarette smoking) RR of PTB for twins of former LBW (compared to non-LBW) African-American mothers equaled 1.2 (1.1-1.4). In contrast, the adjusted RR of SGA among former LBW (compared to non-LBW) African-American mothers equaled 1.1 (0.8-1.5). Former LBW White mothers (n = 105) had rates of PTB and SGA among twins similar to that of their former non-LBW peers (n = 2,136), the adjusted RR equaled 1.2 (0.95-1.4) and 1.2 (0.8-1.7), respectively.

CONCLUSION. Maternal LBW is a modest risk factor for PTB, but not SGA, among African-American twins. A similar phenomenon fails to occur among White mothers. This findings support a life-course conceptual model of the racial disparity in PTB rates.
Title: Utilization of Emergency Departments for Care of Excessive Menstruation: Analyses Using the Nationwide Emergency Department Sample (NEDS)

Summary: Women with menstrual disorders often access healthcare through the emergency department (ED) even though many of their complaints can be addressed in the ambulatory setting. We investigated the health care utilization of women seeking evaluation for excessive menstruation across emergency departments in the United States.

Sample: This cross-sectional study used the NEDS collected by the Healthcare Cost and Utilization Project from 2009-2011.

Methods: Data analysis was based on the total weighted sample of women with either a primary or secondary ICD-9 code of 626.2 (excessive or frequent menstruation). Statistical analysis included weighted frequencies to account for complex sampling design and to allow for national estimates. Multivariable logistic regression was used to examine factors associated with admission.

Results: There were 225,069 encounters for excessive menstruation from 2009-2011. 86.1% of encounters resulted in treatment and release from the ED, with 13.2% resulting in admission to the same hospital. The mean age was 31.8 years (SE 0.05), with 34.5% of encounters from zip-codes with median household income <$40,000. The most common primary payer was private insurance (35.4%) followed by Medicaid (30.7%) and self-pay (25.0%). The average total charges to ED services were $2,343 (SE $17.08). Excessive menstruation encounters cost a total of $416 million over the three years. Women presenting from zip codes with the highest median household income quartile were more likely to be admitted than those from the lowest income quartile (Adjusted OR 1.35 95% CI: 1.30-1.40).

Conclusion: The majority of ED visits for excessive menstruation resulted in discharges from the hospital. While the ED is often perceived as an easier and more visible access point for health care, helping women seek care in the appropriate settings could improve healthcare delivery and efficiency.
Title: Building an Academic Medical Center-Faith Based Organization Research Partnership to Improve Health by Using Women’s Feedback

Summary: Faith based organizations are trusted members of communities and have been sought by academic medical centers to engage under-represented research cohorts. Although partnering with faith based organizations can diversify research participation, there are limited data on the recruitment biases that can result from these partnerships.

Objective: To determine the demographic factors associated with research participation among women in an academic medical center-faith based organization partnership.

Sample: A total of 328 completed surveys were obtained from African American women in a community fair in Chicago, IL.

Methods: A convenience sample was obtained from attendees at a community fair hosted by a faith based organization in Chicago, IL. Participants completed a survey which included demographic data and previous/future research participation. Qualifying participants were English-speaking women aged 18 and older who finished >50% of the survey.

Results: 328 women completed the survey. 95% were African-American. Subjects had a mean age of 51.4 ± 12.8 years. The majority had health insurance (76.2%), had seen a primary care physician within the last year (84.1%), and felt confident filling out medical forms (64.6%). 47% of participants had participated in research and 76% were interested in future research participation. Chi-square analysis revealed that having been seen by a doctor within the last year (p< 0.001) and positive health condition (p<0.001) were associated with interest in research participation. Confidence in filling out medical forms was associated with both past research participation (p=0.03) and interest in future research participation (p<0.001).

Conclusion: Being seen by a doctor within the last year, positive health condition, and confidence in filling out medical forms are factors associated with interest in future research participation. These data are helpful in understanding the potential bias that exists in community recruitment. While an academic medical center-faith based organization partnership is an excellent means of diversifying a research population, it may attract a healthier, more health literate subgroup within the target population.
Title: 4R (Right Information and Right Care to the Right Patient at the Right Time) for Guideline Indicated BRCA Testing of Newly Diagnosed Breast Cancer Patients

Objective: The timing of genetic risk assessment and testing has a large impact on treatment decisions for genetic cancers. Though BRCA mutation status has an important impact on preventive and treatment decisions, there are low rates and inappropriate timing of genetic counseling referrals for indicated women based on family cancer history. This study was a pilot test of an intervention to identify women at risk for genetic cancer as early as possible and provide information on how to access genetic counseling services. The primary outcome of the study was improved uptake and timing of genetic counseling and testing services amongst participants with elevated hereditary breast and ovarian cancer (HBOC) risk.

Sample: Eligible patients for the study were women age eighteen or older, who speak English, are of any race or ethnicity, and present to the Lynn Sage Breast Center at Northwestern Prentice Women’s Hospital for a mammogram. This is a non-probability convenience sample of patients, and as such there is no sampling frame in this study.

Methods: Consented participants at the Lynn Sage Breast Center at Northwestern Prentice Women’s Hospital were given a short questionnaire to assess risk status and tailored letters containing information about accessing relevant genetic counseling services. Participants were followed via electronic medical record to measure how many accessed the recommended services, how long it took them to do so, and any subsequent treatments they pursued.

Results: A total of seventy-five women were recruited for the pilot test. Sixty-seven participants (90%) had no experience with prior genetic counseling and BRCA testing. Over the three month follow-up period, no participants accessed the recommended genetic counseling services. Descriptive analysis on the questionnaire data was performed to examine response trends. Of this group of sixty-seven, forty-four participants (65%) had a family history of breast, ovarian, or pancreatic cancer. The most common characteristics among this group of patients were: a family member or themself diagnosed with breast cancer at or under age 45 (15%), and having two or more relatives diagnosed with breast cancer on the same side of the family (28%). Participants in each of these groups were more likely to also experience: a family member diagnosed with bilateral breast cancer or pancreatic or prostate cancer; or a family member diagnosed with ovarian, fallopian, or primary peritoneal cancer. Additionally, the questionnaire response data indicate participant confusion or lack of knowledge on three specific questions.

Conclusions: The majority of women in the study had a family or personal history of cancers, which indicates that women chose to participate based on their family or personal history. This is expected, as the questionnaire was created based on knowledge of common medical history characteristics of HBOC. Seeing these trends among a group of women who are likely at higher risk of genetic cancer provides a preliminary measure of internal validity of the questionnaire. Follow up on study patients is currently ongoing to assess the impact of the intervention. If successful, this could provide an efficient, standardized tool that could be implemented in any healthcare setting to create population-level improvements in women’s health.
Title: Career 911: Your Future Job in Medicine and Healthcare

Summary: Health disparities have been linked to underrepresentation of minorities in healthcare careers. Building a diverse healthcare workforce warrants efforts to boost access to health careers education for nontraditional students. Massive open online courses (MOOCs) – available to anyone with an internet connection – have the potential to impart interdisciplinary knowledge and skills toward students’ pursuits of health related careers. We present the development of *Career911: Your Future Job in Medicine and Healthcare*, a MOOC aimed to help high school students, recent graduates, and those considering career transitions explore healthcare career options and learn strategies for entry into the healthcare field, such as preparing a career portfolio. Woven throughout are personal stories and “day in the life” narratives of health professionals.

Methods: Developed by an interdisciplinary team of faculty, students, healthcare professionals, instructional designers, and digital media specialists, the course will be piloted on the Coursera platform over a 6 week period. Throughout the development process, we have built partnerships with representatives from local high schools, community colleges, and organizations to integrate the curriculum into existing programs.

Results: We anticipate an enrollment of over 3,000 students, from over 100 different countries. During the pilot, we will gather log data with respect to student enrollment, demographics, usability, engagement, and retention. Qualitative interviews with educators and students will provide in-depth insights on application of the course on next career steps.

Conclusion: This MOOC offers interdisciplinary health career curricula to diverse populations, with potential to diversify the healthcare workforce and impact health equity globally.