

Annual University of Michigan Paper Day
May 4, 2005

Title: Implementation of cystic fibrosis screening at the University of Michigan
Authors: Bauer ST, Hanlon-Lundberg KM

Objective: Cystic fibrosis carrier screening was implemented at the University of Michigan based on the 2001 ACOG/ACMG guidelines. Implementation of prenatal cystic fibrosis screening was evaluated by observing adherence to screening guidelines, impact on obstetrical management (incidence of prenatal testing and pregnancy termination), and program cost.

Methods: After IRB approval, prospective chart review identified patients who had prenatal CF screening. Data was collected from March 2002 through February 2004. Medical records were reviewed for correlative demographic and pregnancy outcome data. Ethnicity was by self-identification.

Results: During the study period, 7781 patients were delivered. 29 couples were at risk for CF based on family history in one or both partners and were not evaluated as a part of this study. 24.5% of Caucasian couples were screened who would not have been offered testing prior to this program. 13.5% of non-Caucasians patients and 2.1% of unspecified ethnicity were tested. 82% of patients screened were considered "at risk" for being a CF carrier based on Caucasian ethnicity. Six of 203 non-Caucasian patients screened positive for CF mutations (carrier frequency 1:33). No patient had amniocentesis for CF testing after having one/both parents identified as a carrier.

Conclusion: Prenatal screening for cystic fibrosis becomes cost effective through prevention of the birth of affected individuals; however, no patient underwent prenatal testing or pregnancy termination for CF status at our institution during the first two years of CF screening. We observed a fairly a high prevalence of carrier status among both Caucasians and non-Caucasians. Study of CF screening implementation continues.

Title: Maternal and neonatal outcomes following Vaginal Birth After Cesarean (VBAC) vs Spontaneous Vaginal Delivery (SVD)

Authors: Brincat C and Fenner D

Background: Few issues in obstetrics are more controversial than the when and why of cesarean delivery. Most studies have compared outcomes in patients who have undergone a trial of labor after cesarean to those pursuing an elective repeat cesarean delivery. Few studies have compared the outcomes of those completing a trial of labor to their spontaneous vaginal delivery counterparts. In doing so, we are better able to understand what is meant by a "successful" VBAC.

Methods: We reviewed the charts of VBAC patients from 2004, abstracting for demographics, labor course and complications. VBAC patients were matched to women having a spontaneous vaginal delivery (SVD) controlling for parity, senior staff and resident. When not possible to match exactly by senior staff or resident, deliveries were matched always by parity and at least by practice group. These two groups were compared by means of multivariate logistic regression ($p < .05$) to detect predictors of the labor course and its complications. Minor complications included: chorioamnionitis, shoulder dystocia, hemorrhage without transfusion, and three or more lacerations, while major complications included: operative repair, infant to NICU, and hysterectomy.

Result(s): One hundred forty-two patients were included, 71 out of the 88 VBAC patients who delivered in 2004, and their 71 SVD counterparts. There was no difference between VBAC and SVD mothers in age, race, BMI, infant birth weight, or APGAR scores. Backwards stepwise linear regression determined that women who completed a VBAC were statistically more likely to experience a complication ($\beta=1.318$, $p=.008$) based on their mode of delivery.

	VBAC	NSVD	P value
Episiotomy	12 (17%)	8 (11%)	.335
2° laceration	39 (55%)	35 (51%)	.618
3° laceration	8 (11%)	3 (4%)	.125
Operative delivery	2 (3%)	2 (3%)	1.0
Complications	26 (37%)	12 (17%)	.008
Complications-minor	24 (34%)	12 (17%)	.021
Complications-major	16 (23%)	9 (13%)	.123

Conclusions: "Successful" VBAC is typically described as a vaginal birth, regardless of the consequences to mother or baby. Our study found that women who undergo a successful VBAC were nearly three times more likely to sustain a third degree laceration. Furthermore, we found that VBAC patients were statistically more likely to experience a complication as a direct result of mode of delivery. Discussion of these risks involved in a successful VBAC is a key component of good informed consent.

Title: Persistent or recurrent labial agglutination: Is surgery the only option?
Authors: Kumetz L, Quint EH and Smith YR

Objective: Labial agglutination is a common vulvar problem in children. Topical estrogen is generally the first line therapy. The objective of this study is to review the recurrent or persistent cases of labial agglutination treated at the University of Michigan to determine the success rate of conservative medical management and indications for surgery.

Design: Retrospective Chart Review

Materials and Methods: Girls seen at the University of Michigan pediatric and adolescent gynecology clinic between 1996 and 2004 for labial agglutination were identified based on clinical diagnosis. The parents of each patient treated with estrogen received explicit instructions and demonstration of estrogen application, combined with gentle traction perpendicular to the line of fusion. Parents were counseled that if the agglutination resolved in 4 weeks, no follow-up was necessary. The records were reviewed for age, length of time of symptoms, previous treatments, results of topical estrogen therapy, and indications for surgery.

Results: Sixty-seven girls with labial agglutination were considered for the study. Forty-eight were cases of recurrent or persistent disease. The average age at presentation was 4.1 years (range 0.6 – 16 years). The average length of time that labial agglutination had been present was 2.1 years (range 2 weeks – 11 years.) Within those 48 girls, 40 (83.3%) had been treated with topical estrogen, 5 (10.4%) had been treated with topical estrogen and manual separation, 1 (2.1%) was treated with oral and topical estrogen, and 2 (4.2%) were treated with manual separation only. In 19 (39.6%) girls urinary symptoms were also present. Results of topical estrogen therapy include: 15 opened either partially or completely, 9 required surgery, and 19 did not follow up. Of the 14 who underwent surgery, 5 received surgical therapy initially after having failed outside therapy, and 9 failed our topical estrogen treatment. The reasons for failure of our treatment include: 2 girls were uncooperative with topical application, and 7 failed to improve. Of the 5 girls who were brought to the OR initially, 3 parents had declined further topical treatment, 1 patient presented with acute urinary obstruction, and 1 patient had almost complete agglutination, therefore surgery was recommended.

Conclusions: Our study suggests that re-treatment of persistent or recurrent labial agglutination with topical estrogen and detailed application instruction leads to avoidance of surgical intervention in at least 34.9% and up to 79% of cases. Even in patients who previously required surgery, an attempt at conservative medical management should be considered.

TITLE: Pharmacokinetics of Vancomycin in pregnancy
AUTHORS: Laiprasert J, Klein KD and Pearlman MD

Background: Group B Streptococcus (GBS) intrapartum antimicrobial prophylaxis is used routinely across the United States to prevent GBS disease. For patients with serious penicillin allergies and who are colonized with clindamycin resistant GBS, vancomycin is the recommended chemoprophylactic agent. There are no data regarding the pharmacokinetics of vancomycin in pregnant women and it is unknown whether or not vancomycin reaches the fetal compartments (blood and amniotic fluid) in therapeutic levels.

Methods: Sixteen women undergoing elective cesarean delivery were to be allocated to receive one gram of vancomycin intravenously ½, 1, 4, or 6 hours prior to delivery. Infusion time was 90 minutes. Subjects were without any significant infection or cardiovascular, liver or renal disease. Samples of maternal blood, amniotic fluid and fetal cord blood were collected at time of delivery. Exact collection times relative to the completion of the vancomycin infusion were noted. Vancomycin levels were measured using a fluorescence polarization technique. Informed consent was obtained in this IRB approved study.

Results: Thirteen women were enrolled; intervals from drug infusion completion to delivery varied from 30 to 465 minutes. Timing from drug administration to delivery varied from the original planned interval; therefore, data were analyzed individually by interval of time from completion of administration to time of delivery. The generally accepted breakpoint for vancomycin against GBS is 1 mcg/mL. Interim data analysis indicates that cord blood concentrations remain above the 1 mcg/mL breakpoint for at least 60 minutes following administration of 1 gm of vancomycin. In addition, 53.8% (7/13) of the subjects had some manifestation of Red Man's syndrome during their administration, with 7.9% (1/13) rate of moderate symptoms (hypotension and shortness of breath). No long term sequelae were noted in any study subjects or their fetuses.

Conclusions: Vancomycin does appear to cross the placenta according to first order kinetics, in contrast to predictions of previously published data in an ex-vivo placental model. These levels do appear to be therapeutic for GBS prophylaxis. Adverse effects associated with vancomycin are frequent. This information suggests that vancomycin can be used for group B streptococcus prophylaxis in patients with anaphylactic penicillin allergy, but further study is warranted.

Title: Sulindac inhibits NF-kB activation and induces apoptosis in ovarian cancer cells

Authors: Rasool N, Fogoros S, Choi M, Tan L, and Rebecca Liu JR

Background: NSAIDs, including sulindac have known chemopreventive and anti-tumorigenic properties. The NF-kB pathway is believed to be involved in this chemopreventive mechanism. NF-kB inhibitors, such as sulindac decrease prostaglandin synthesis by inhibiting the activity of cyclooxygenase. Induction of COX2 by inflammatory cytokines or hypoxia-induced oxidative stress can be mediated by nuclear factor kappa B (NF-kB).

Methods: A panel of ovarian cancer cell lines, (including both mutant and wild type p53 expressing cell lines) were screened for constitutive activation of NF-kB. Cells were treated with DMSO (control), sulindac or cisplatin. Growth inhibition was determined by sulfurhodamine assay and cell viability was determined by propidium iodide permeability staining, followed by analysis by flow cytometry. To assess whether sulindac could inhibit NF-kB activation, cells were transiently transfected with an NF-kB luciferase reporter plasmid, treated with sulindac or DMSO (control), and luciferase expression was determined. To determine if sulindac treatment resulted in alterations in COX expression, treated cells were harvested, lysates were prepared, and immunoblotting was performed to determine COX-1 and COX-2 protein expression.

Result(s): Sulindac induced growth inhibition and cell death in chemoresistant and chemosensitive ovarian cancer cell lines, regardless of p53 status. Sulindac inhibited activation of NF-kB in p53 wt and mt cell lines, however the effect was more pronounced in the p53 wt cell lines. COX2 expression was diminished following treatment with Sulindac.

Conclusion(s): Sulindac inhibits ovarian cancer cell growth and induces cell death in ovarian cancer cells regardless of p53 status. Treatment of ovarian cancer cells with sulindac results in decreased NF-kB activity and COX-2 expression. NF-kB inhibitors such as sulindac may play a role in the treatment and/or prevention of ovarian cancer.

Title: Vulvodynia: Is there an increased incidence of somatic/gastrointestinal symptoms?

Authors: Sangeeta S, Dalton V, Reed B and Haefner H

Background: Vulvodynia has remained an enigma to most clinicians with regard to both diagnosis and treatment. Pain syndromes in general have been linked to both increased psychological symptoms including anxiety and depression, as well as somatic syndromes such as irritable bowel syndrome. In review of the literature there is some suggestion of an increased incidence of depression in women with vulvodynia. Little has been reported in terms of an association with other somatic and/or gastrointestinal symptoms in women plagued with vulvodynia. The goal of this study is to examine whether there is an increased incidence of somatic and/or gastrointestinal symptoms in women with vulvodynia, compared to women with other vulvar complaints.

Methods: The study subjects were drawn from a pool of patients that presented to the University of Michigan Center for Vulvar Diseases from 1993 to 2003. After IRB approval was obtained, a chart review was performed of an initial standardized history form of this population of women. Cases included those that had a diagnosis of vulvodynia of unknown etiology; controls included those who had a variety of other diagnoses explaining their vulvar complaints. Data were collected on demographic information, as well as on symptoms of headache, stomach pain, heart palpitations, nausea, diarrhea/ constipation, dizziness, gastrointestinal ulcer disease, and urinary symptoms. Analyses included Pearson Chi-square and t-tests for univariate assessment, and logistic regression to control for potential confounders.

Result(s): A total of 867 patients' histories were reviewed. Comparisons were made between the patients with vulvodynia and the control population. There were no significant differences in education, ethnicity, or income levels of the groups. Patients with vulvodynia were found to have an increased incidence of stomach pain, nausea, and diarrhea/constipation ($p < 0.05$), and these differences were not explained by education, ethnicity, or income levels. There was no significant difference between those patients with vulvodynia and those with other diagnosed vulvar disorders in the other somatic symptoms assessed.

Conclusion(s): Women with vulvodynia for the most part do not have an increased incidence of somatic symptoms compared to those with other diagnosed vulvar conditions. When specifically looking at gastrointestinal symptoms, there does seem to be an increased incidence in women with vulvodynia.

Title: Risk factors for breakdown of laceration/episiotomy repair following vaginal delivery
Authors: Williams MK and Chames MC

Background: Perineal laceration breakdown after vaginal delivery, although an uncommon occurrence, represents a source of significant morbidity to those patients affected. Because of its low incidence, it has been poorly studied. Our objective was to identify risk factors associated with perineal laceration breakdown in the postpartum period.

Methods: An IRB approved, retrospective, case controlled study was performed reviewing perineal laceration breakdown in all patients delivering over the last 10 years at the University of Michigan. Both inpatient and outpatient diagnostic code databases were used to identify cases. Two to one control to case matching was performed using data from patients with vaginal lacerations of at least second degree or an episiotomy, both midline and mediolateral. Inpatient and outpatient records pertaining to prenatal care, delivery, and postpartum care were reviewed for the presence of potential antepartum and intrapartum risk factors for breakdown.

Results: Fifty-nine patients from September 1995 to February 2005 were identified as having a breakdown of a laceration repair out of a total of 19,067 patients. One hundred eighteen matched controls were identified over the same time period. Patients with breakdowns had a longer second stage ($p=0.001$), were more likely to have meconium stained amniotic fluid (OR 3.0, 1.1-7.9), mediolateral episiotomy (OR 6.9, 2.6-18.7), or a third or fourth degree laceration (OR 3.1, 1.5-6.4). Instrumented vaginal delivery was not significantly related to laceration breakdown after controlling for mediolateral episiotomy. Prior vaginal delivery was protective (OR 0.38, 0.18-0.84). Patients who had a spontaneous laceration were no more likely to breakdown than those who had an episiotomy. There was no correlation with smoking, age, BMI, birth weight, duration of rupture of membranes, diabetes, chorioamnionitis or type of suture used for repair.

Conclusions: Antepartum risk factors did not appear to play a significant role in the occurrence of breakdown of laceration repair after delivery. The most significant intrapartum events were mediolateral episiotomy, third and fourth degree lacerations, meconium exposure, and increased length of second stage.