



The American College of Obstetricians and Gynecologists

Papers on Current Clinical and Basic Investigation

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Contents

Papers on Current Clinical and Basic Investigation

Tuesday, May 5, 2009

2:00pm – 2:10pm

Retrieval of Trophoblast Cells from the Cervical Canal for Prediction of Abnormal Pregnancy

Anthony N. Imudia, Yoko Suzuki, Brian A. Kilburn, Frank D. Yelian, Michael P. Diamond, Roberto Romero, D. Randall Armant

2:10pm – 2:20pm

Dietary Impact on Endometriosis: A Closer Look at the Active Ingredients of Red Wine and Soy

Sharai C. Amaya, Christina Jacobson, Angela Houwing, Bruce A. Lessey

2:20pm – 2:30pm

Contraceptive Effectiveness of Oral Contraceptives: The Impact of a 24-Day Regimen

Juergen Dinger, Anita Assmann, Carolyn Westhoff

2:30pm – 2:40pm

Cesarean Section Rates and Medical Liability Climate

Elizabeth A. Platz, Scott Sullivan, Roger Newman, Greer Albergotti

2:40pm – 2:50pm

Racial and Ethnic Disparities in the Outcome of IVF Cycles Using Donor Oocytes in the United States

Tarun Jain, Gary Jeng, Mark D. Hornstein, David Grainger, Jeani Chang, Maurizio Macaluso

2:50pm – 3:00pm

Is Testing Necessary Prior To Methotrexate Administration for Treatment of Ectopic Pregnancy

Terry S. Dunn, Mona Krull, Sara Mazzoni

3:00pm – 3:10pm

Human Papillomavirus (HPV) Vaccination Rates and Attitudes of First Year College Females

Laura A. Carr, Jennifer L. Young, Susan C. Modesitt

3:10pm – 3:20pm

Pregnancy Outcomes Associated with Nasopharyngeal Carriage of MRSA

Rupesh Patel, Howard Kaufman

3:20pm – 3:30pm

In Search of Obstetric Quality Outcome Measures: An Analysis of the Adverse Outcomes Index (AOI)

Thomas J. Benedetti, Thomas P. Strandjord, Suzan Walker

3:30pm – 3:40pm

Ten Year Episiotomy Trends among Different Practice Groups at a Teaching Hospital

Cynthia E. Johnson, Eugene Declercq, Mary K. Barger, Lisa M. Sullivan

3:40pm – 3:50pm

Dollar Store Pregnancy Tests: How good are they?

Sunania Sehwani, Jullian Zovko, James N. Anasti

3:50pm – 4:00pm

Gene Expression Profiling of Vaginal Tissue in Women With and Without Pelvic Organ Prolapse

Jennifer B. Pugliese, Gerald B. Taylor

DONALD F. RICHARDSON MEMORIAL PRIZE PAPER

Retrieval of Trophoblast Cells from the Cervical Canal for Prediction of Abnormal Pregnancy

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OBJECTIVE: Identification and quantification of fetal trophoblast cells in the cervical canal during the first trimester to assess their usefulness to predict an abnormal pregnancy.

MATERIALS AND METHODS: Patients, age 18-45, presenting with a normal intrauterine pregnancy (IUP; n=37), symptoms of ectopic pregnancy (EP; n=10) or blighted ovum (BO; n=5) were enrolled for collection of transcervical specimens using a commercial PAP test. Non-pregnant, nulliparous women (n=7) were included as negative controls. Cells were cleared of mucus by acidification, prepared on microscope slides and labeled with a monoclonal antibody recognizing HLA-G, a major histocompatibility complex antigen specifically expressed by trophoblast cells. HLA-G positive and negative cells were counted to calculate the ratio of trophoblast cells to total cervical cells.

RESULTS: Trophoblast cells were observed in 35/37 normal IUP, 6/10 EP and 4/5 BO specimens. The average frequency of HLA-G positive cells in the normal IUP cervical samples was approximately 1 in 2000, which was 4 to 5-fold higher than samples from patients with EP or BO (p<0.001). The latter two groups did not differ significantly. A receiver operating characteristic analysis showed that EP and BO pregnancies were distinguishable from normal pregnancies with 93% sensitivity, 95% specificity, 97% positive predictive value and 87% negative predictive value. There were no related complications to the ongoing normal IUP.

CONCLUSION: Trophoblast cells can be reliably identified among cervical cells in the first trimester by immunohistochemical staining for HLA-G. Abnormal pregnancies are predictable based on the abundance of trophoblast.

DONALD F. RICHARDSON MEMORIAL PRIZE PAPER

Dietary Impact on Endometriosis: A Closer Look at the Active Ingredients of Red Wine and Soy

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OBJECTIVE: To test the hypothesis that dietary soy and ingredients in red wine act as anti-estrogens, we used both in vivo and in vitro models to examine the effect of genistein and resveratrol on endometrial proliferation and activation.

STUDY DESIGN: Laboratory analysis of the well-differentiated cell line ECC-1 and immunocompromized mouse model RAG-2/gamma(c) exposed to genistein and resveratrol. In cell line studies, we examined the estrogen-induced protein, alkaline phosphatase and investigated the effect of genistein and resveratrol on the ERE-luciferase. In the mouse model, we implanted human endometrium or endometriosis into ovariectomized RAG-2 mice and treated them with estradiol, estradiol plus progesterone, or estradiol plus genistein or resveratrol using 3 different doses of compound.

RESULTS: The ECC-1 cell line proved useful for the development of the alkaline phosphatase assay of Littlefield, demonstrating estrogenic activity by estradiol or DES and anti-estrogenic activity of progesterone. Like genistein, resveratrol demonstrated anti-estrogenic activity in this assay. The antagonistic actions of resveratrol were similar to that seen with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), alone or in combination with estradiol. Using ERE-luciferase reporter genes constructs, we demonstrate that both genistein and resveratrol inhibited estradiol action at the ERE site, although this activity was weak. In mice treated with estradiol, xenografted fragments of human endometrium or endometriotic tissues were established showing elevated ER-alpha and proliferative activity (Ki67 immunostaining). By comparison, concomitant treatment with progesterone, genistein and resveratrol appeared to reduce the size and activity of the tissue in a dose responsive manner, although statistical significance was only reached for proliferation in the highest concentration resveratrol group (60 mg dose).

CONCLUSION: These studies confirm that resveratrol functions as an anti-estrogen using both in vivo and in vitro assays of estrogen activity. The RAG-2 immunocompromized mouse is an excellent model to examine the hormonal response of human endometrium and endometriotic tissues, in vivo. Resveratrol may be functioning as an AhR antagonist. Further studies are required in humans to investigate the role of dietary compounds such as soy (genistein) or red wine (resveratrol) on both gynecologic health and disease.

Contraceptive Effectiveness of Oral Contraceptives: The Impact of a 24-Day Regimen

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OBJECTIVE: To investigate the contraceptive effectiveness of a 24-day regimen of 3mg drospirenone (DRSP)/20mcg ethinylestradiol (EE) compared with a 21-day regimen of DRSP/EE and OCs containing other progestins.

METHODS: This is an international, prospective, controlled, non-interventional cohort study with three study arms: 24- and 21-day regimens of DRSP/EE, and OCs containing other progestins. The study was started in the USA and will be extended to several European countries in the fourth quarter of 2008. New users of an OC (starters or switchers) are being recruited by a network of gynecologists. A 3–5 year follow-up of more than 80,000 women should be sufficient to document more than 150,000 women-years. Baseline and follow-up information are being collected via self-administered questionnaires. A multifaceted follow-up procedure will ensure a low loss-to-follow-up rate. Inferential statistics are based on Cox regression models comparing the cohorts.

RESULTS: At March 2008, 434 unwanted pregnancies were observed. Pearl Indices for the 24- and 21-day regimens of DRSP/EE, and for OCs containing other progestins were 0.94 (95% CI: 0.66–1.30), 1.50 (95% CI: 1.06–2.05), and 2.22 (95% CI: 2.00–2.45), respectively. The adjusted (age, educational level, parity, etc.) hazard ratios for the 24-day vs. the 21-day regimen of DRSP/EE and for the 24-day regimen of DRSP/EE vs. OCs containing other progestins were 0.60 (95% CI: 0.38–0.95) and 0.45 (95% CI: 0.32–0.64), respectively.

CONCLUSIONS: Interim results indicate that a 24-day regimen of DRSP/EE has higher contraceptive effectiveness under routine medical conditions than a 21-day regimen of DRSP/EE or OCs containing other progestins.

Cesarean Section Rates and Medical Liability Climate

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OBJECTIVE: To determine whether state specific cesarean section delivery rates differ by classification of the medical liability climate.

STUDY DESIGN: This was a cross-sectional observational study, utilizing population level data. Cesarean section rates for 2004 were obtained from the National Center for Health Statistics natality database. Individual states were classified as either “in crisis”, “crisis brewing” or “not in crisis” by a formula utilized by ACOG in 2004. State demographic and population data was obtained from the United States Census bureau and NCHS. Statistical analysis included bivariable associations which were analyzed utilizing Pearson correlations and a multivariable step-wise linear regression. This model was fit and adjusted based on variables found to be associated with cesarean delivery rates in the bivariable analysis.

RESULTS: There were 14 states categorized as “in crisis”, 8 as “crisis brewing” and 28 as “not in crisis” by ACOG’s medical liability climate. In 2004 the mean state cesarean rate was 28.1 % with a range of 20.4% to 34.9%. Increasing cesarean section rates correlated with states classified as “in crisis” or “crisis brewing”. ($R=0.36$, $p<.01$) In the regression model, variables retaining their significant association with cesarean section rates included medical liability classification ($p<.009$), obesity ($p<.0001$) and population density ($p<.001$).

CONCLUSION: States classified as having either a current medical liability crisis or crisis brewing by ACOG demonstrate significantly higher rates of cesarean sections even after controlling for other known risks for cesarean delivery. This may reflect a pattern of ‘defensive’ medicine in response to liability concerns.

Racial and Ethnic Disparities in the Outcome of IVF Cycles Using Donor Oocytes in the United States

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Gary Jeng, PhD, Mark D. Hornstein, MD, David Grainger, MD, Jeani Chang, MPH, Maurizio Macaluso, MD

OBJECTIVE: Asian and Black women undergoing IVF using their own oocytes have poorer outcomes compared to White women. This study assesses if these negative outcomes could be overcome by use of donor oocytes.

METHODS: Retrospective study of 2004-06 U.S. ART data, compiled annually by the CDC. Cumulative logit model with adjustment for maternal history, infertility diagnosis, and treatment factors was used to compare IVF outcomes between different races.

RESULTS: In 2004-06, 29,948 fresh donor oocyte IVF cycles without use of a gestational carrier were available for analysis. 60% of these cycles without an indication of multiple-ethnicity were analyzed. Table 1 summarizes findings before adjustment of significant confounders. With the adjustment, compared to White women, Black women were more likely to have a failed cycle prior to embryo transfer (odds ratio (OR): 1.36, 95% CI: 1.10-1.67), less likely to achieve a pregnancy (OR: 0.69, 95% CI: 0.69-0.80), and less likely to have a live birth (OR: 0.65, 95% CI: 0.56-0.75). Asian and Hispanic women, however, did not significantly differ from White women in these outcomes.

CONCLUSION: Relative to White women, Black women undergoing IVF using donor oocytes have worse outcomes that cannot be accounted for by uterine or tubal disease. Asian and Hispanic women, however, have comparable outcomes to White women.

Table 1:

Variable	Racial and Ethnic Groups				P Value
	White	Asian	Black	Hispanic	
%					
# cycles (N)	14605	1484	959	899	
Prior ART	54.8	55.3	44.8	45.5	< 0.01
Prior pregnancy	53.7	41.4	52.8	49.6	< 0.01
Uterine factor	4.3	5.2	13.5	5.7	< 0.01
Tubal factor	8.3	6.1	17.1	19.7	< 0.01
# Embryos transferred					< 0.01
One	4.5	3.8	3.2	3.7	
Two	65.2	65.0	63.8	56.8	
Three	24.8	24.9	22.6	27.7	
Four or more	5.5	6.3	10.4	11.8	
Cycle Cancellation	5.8	5.1	7.8	6.0	0.06
Clinical Pregnancy	56.6	55.6	46.1	53.8	< 0.01
Miscarriage per pregnancy	13.2	16.4	19.2	16.1	< 0.01
Live births (LB)	48.9	46.2	36.9	44.8	< 0.01
LB: tubal factor only	43.3	42.3	32.4	33.7	0.04
LB: uterine factor only	48.2	45.3	36.6	52.5	0.07
LB: excluding uterine & tubal factor	49.5	46.4	38.6	47.2	< 0.01

Is Testing Necessary Prior To Methotrexate Administration for Treatment of Ectopic Pregnancy

Terry S. Dunn, MD
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OBJECTIVE: To evaluate the necessity of pre-treatment laboratory testing prior to administration of methotrexate for ectopic pregnancy.

METHODS: The charts of all women treated for ectopic pregnancy from 09/2001 – 09/2006 were reviewed. Demographic data including age, tobacco use, history of IUD use, previous ectopic pregnancies, sexually transmitted diseases and medical co-morbidities were recorded. Laboratory values of HCG, liver and renal function, pre and post treatment were extracted. Statistical analysis was performed in SPSS Version 1. A p value less than .05 was considered significant.

RESULTS: 285 patients were treated for ectopic pregnancy during this time period; 167 patients with methotrexate and 118 with surgical intervention. In the methotrexate group; the average dose was 87.2 mg with an average HCG of 3,241. The demographics in each group were not significantly different, except for alcohol use ($p < .05$) and age ($p = .028$). 95% of patients in the methotrexate group had laboratory tests drawn prior to treatment; 11% of patients had abnormal liver function tests (AST, ALT), .7% had an abnormal creatinine. The only significant variable associated with an abnormal tests were medical-comorbidities ($p < .001$). There were no patients who were not treated secondary to abnormal values. Laboratory testing cost three hundred and ninety dollars per patient.

CONCLUSION: Pretreatment laboratory testing did not affect the administration of methotrexate. A significant cost savings to the health care system could be appreciated by deleting this testing from the ectopic protocols.

Human Papillomavirus (HPV) Vaccination Rates and Attitudes of First Year College Females

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OBJECTIVE: The purpose of this study was to determine the prevalence of human papillomavirus (HPV) vaccination among entering female college students. In addition, the survey investigated perceived barriers to receiving the HPV vaccine and HPV knowledge.

METHODS: A 30-item self administered anonymous questionnaire was emailed to all entering female college students at the University of Virginia using the online survey platform SurveyMonkey.com®(Portland, OR).

RESULTS: Of eligible participants, 396 of 1,668 (23.7%) completed the survey. A total of 97.7% of respondents had heard of the HPV vaccine and primarily reported physicians (65.8%) as their source of information followed by parents (61.5%) and television (57.5%). Seventy percent of participants have received at least one dose of the Gardasil vaccine with 46.1% having completed the series. The most important factors resulting in vaccination are physician recommendation (79.4%) and parental approval (76.9%). Unvaccinated participants were three times more likely than vaccinated participants to report safety concerns (64.7% vs 21.4%). Of those with safety concerns, parents and media were cited to be the most influential factors (52.2%, 45.5%). Moral and religious views were not associated with vaccination decision-making. Comparison of vaccination rates between whites and non-whites demonstrated that white first-years are 44% more likely to have been vaccinated than their minority counterparts (RR 1.44, 95%CI 1.17, 1.77).

CONCLUSION: Although the majority of first-year students have received at least one shot, racial disparity between white and non-white students is significant. Results indicate that vaccination practices could widen the gap among whites and non-whites in rates of cervical cancer.

Pregnancy Outcomes Associated with Nasopharyngeal Carriage of MRSA

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OBJECTIVE: MRSA infections have increased significantly over the past decade. Routine screening for MRSA upon hospital admission is increasing. Previous studies examined vaginal culture MRSA status, however nasopharyngeal MRSA status has not been well studied. The objective of this study was to determine if there was a correlation between positive screen results and increased risk of adverse maternal and fetal outcomes.

STUDY DESIGN: All patients admitted to our institution have MRSA screening as part of the admission protocol. A 7 month retrospective chart review was performed. Newborns to screen positive patients received nasal and umbilical MRSA swabs. NICU admissions and neonatal sepsis workups were noted. Maternal postoperative infections and anesthesia related complications were noted. Outcomes were compared to a control group.

RESULTS: A total of 1,045 patients were tested. 31 patients tested positive for an overall incidence of 2.9%. The hospital wide incidence for this overall period was 7.9%. 23 of the patients delivered at our institution. There were no positive neonatal MRSA screens. 13 patients had regional anesthesia administered with no complications or infections noted in the study.

	MRSA Positive	Control	P-Value	Significance
Days Hospital	2.636	2.369	0.405632	Not Significant
5 Min APGAR	8.59	8.57	0.93804	Not Significant
NICU Adm	31.8%	26.5%	0.652542	Not Significant
Sepsis w/u	18.2%	18.4%	0.985351	Not Significant

CONCLUSIONS: Maternal nasopharyngeal carriage of MRSA was not associated with adverse maternal or neonatal outcomes. Regional anesthesia did not increase risk of infection. Based on outcomes, the data does not support routine nasopharyngeal screening of pregnant patients. Further studies are needed with a larger group of patients to help determine optimal management of MRSA positive patients in pregnancy. Future studies will attempt to correlate nasal and vaginal MRSA carriage.

In Search of Obstetric Quality Outcome Measures: An Analysis of the Adverse Outcomes Index (AOI)

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OBJECTIVE: To evaluate the AOI as a metric for quality obstetric care.

METHODS: A State of Washington Perinatal Regional Network quality improvement project to examine the validity and reliability of the AOI was performed. One hospital served as the test site. Administrative data was supplied to the National Perinatal Information Center (NPIC) to calculate AOI. Each of the 10 individual components of the AOI was analyzed to assess whether identified cases fit the clinical definition and for specificity in diagnosis. In 7 categories with less than 100 identified cases, each chart was reviewed and abstracted. In 3 categories with more than 100 cases, a 20% random sample of charts was abstracted.

RESULTS: 42 months data were analyzed. In 4 of the 10 categories there was significant misidentification of cases (false positives): Neonatal Death 2/2 (100%); Inborn Birth Trauma 11/33 (33%); Uterine Rupture 3/7 (43%); and Maternal Return to the OR 17/33 (51%). In a 5th category, NICU admit of term infant, only 74 of 222 cases (33%) were correctly identified. In the other 5 categories 94-100% of cases identified were correctly selected (Maternal Death, maternal ICU admit, Apgar <7, Maternal Blood Transfusion, Perineal Tear). For several indicators the cases selected by algorithm designated administrative codes did not match common clinical definition of the indicators.

CONCLUSION: The AOI, without individual case analysis, data validation and algorithm revision of some components, is not an optimal tool for comparison of quality among hospitals or to monitor quality in a given hospital.

Ten Year Episiotomy Trends among Different Practice Groups at a Teaching Hospital

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OBJECTIVE: We examined how episiotomy rates in a large, urban, teaching hospital are affected by hospital policy recommendations and/or well-publicized publications of episiotomy outcome research.

METHODS: An electronic intrapartum database was used to examine episiotomy rates at a large teaching hospital for 61,268 women with a singleton, vertex fetus at a gestational age of 36 weeks or more from 1997 to 2006. Results were examined by practice type (hospital-based, multi-specialty group, and private practice), obstetricians versus certified nurse midwives (CNM), physician gender, and parity. Differences between groups over time and differences in change after key policy publications will be analyzed using ANOVA.

RESULTS: Episiotomy rates dropped 82% (34% to 6%) for physicians over the decade of study while CNMs had lower rates throughout. After a major paper in May 2005, the rate of episiotomy dropped further, particularly for private practitioners. A wide range across physician groups in 1997 of 17 percentage points decreased to 4 percentage points by 2006. Male physicians had higher episiotomy rates than female physicians every year until 2006. Episiotomy rates for women of all parities decreased every year over the 10 year study with higher rates for primiparas throughout, though the differences decreased.

CONCLUSION: Local peer pressure as well as a response to significant research was reflected in substantially decreasing variation in episiotomy rates across provider and patient groups from 1997-2006. Continued study of the impact of major research and hospital guidelines are warranted.

Dollar Store Pregnancy Tests: How good are they?

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OBJECTIVE: To determine the lowest level of hCG detection of Dollar Store urine pregnancy tests (\$1 PT) and to compare the \$1 PTs to a more expensive urinary pregnancy test.

MATERIALS AND METHODS: Pregnancy test kits were purchased from different dollar stores around the Lehigh Valley, PA. Quick Vue {QV} (Quidel Corporation) were provided by the Women's Health Center. Standards were prepared in urine using purified hCG (Pregnyl, 10,000 units) in the following concentrations 0, 10, 20, 25, 45, 100 miU/mL (+/- 2 miU/mL). Five \$1 PT were tested at each level and read by two independent observers. The tests were checked at 3 and 10 minutes. Lastly, 27 \$1 PT and 27 QV tests were exposed to 25 miU/mL hCG (lower limit of QV). Five independent observers recorded the ease of reading each of the 54 tests.

RESULTS: The \$1 PTs were all negative at the 0 and 10 miU/mL hCG. Three of 5 tested at the 20 miU/mL level were positive. All \$1 PTs were positive at all the levels of 25 miU/mL and above. All \$1 PT and QV tests were positive at 25 miU/mL. In addition, 4 of the five observers felt that the \$1 PTs were easier to read than the QV tests.

CONCLUSION: Dollar store pregnancy tests appear to be able to detect hCG at the same low levels as the more expensive QV urinary pregnancy tests. Furthermore, the \$1 PTs appear to be easier to read than the more expensive QV test.

Gene Expression Profiling of Vaginal Tissue in Women With and Without Pelvic Organ Prolapse

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Gerald B. Taylor, MD

OBJECTIVE: Pelvic organ prolapse (POP) is a condition affecting up to 50% of women after childbirth. Despite the high prevalence and known risk factors little is known about its pathophysiology. Recent studies suggest that women with POP have disorders involving collagen and elastin metabolism when compared to women without POP. The purpose of this study was to analyze gene expression of vaginal connective tissue proteins in postmenopausal women with POP. Our ultimate goal is to determine whether some women are genetically predisposed to POP, independent of other apparent risk factors.

METHODS: Vaginal epithelium biopsies were obtained from women undergoing surgery for POP and from controls undergoing surgery for benign gynecologic conditions. Specimens were taken to the Molecular Biology Lab at Cannon Research Center and analyzed using Microarray technology.

RESULTS: 201 genes with a greater than 2-fold change as compared with controls were identified. Of these differentially expressed genes, 69 were up regulated and 132 were down regulated. Nine up regulated and four down regulated genes of interest were identified. Functions of these genes of interest included cytoskeleton protein scaffolding, collagen degradation, elastin fibrin, cell adhesion and protein catabolism; all of which may impact structural support.

CONCLUSION: It is unclear whether these findings represent a cause or a result of POP. Further research is needed to determine whether these genes are specifically related to pelvic organ prolapse and what impact that relationship has on this widespread disorder.