Providing Evidence-based Clinical Information for 20 Years

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Swedish HABITS Is Cancelled

ABSTRACTS & COMMENTARY

HORMONAL REPLACEMENT THERAPY AFTER BREAST CANCER—IS It Safe? (HABITS) began in May 1997, to compare breast cancer survivors treated for at least 2 years with hormone therapy with treatment other than hormones. By September 2003, a total of 434 women had been randomized and, in December 2003, the steering committee of the HABITS study made the decision to stop the trial because there were 26 women in the treated group and 7 in the nontreated group with new breast cancer diagnoses. Three women died of breast cancer in the treated group and 4 in the nonhormone group.

Women with Stage I and Stage II disease were eligible for the study, and tamoxifen treatment (but not tibolone) was allowed. The safety analysis indicated a relative hazard of 1.8 (CI, 1.03-3.1). The accompanying editorial stated that the HABITS trial "will probably be the last word" on the use of hormone therapy in women with breast disease, and that clinical decisions should hinge on the HABITS conclusion that hormone therapy, even short-term, is associated with an unacceptably high risk of breast cancer recurrence. (Holmberg L, Anderson H. *Lancet*. 2004;363:453-455; Chlebowski RT, Col N. *Lancet*. 2004;363:410-411.)

COMMENT BY LEON SPEROFF, MD

Prior to this publication, the information in the literature regarding hormonal treatment in breast cancer survivors has been uniformly reassuring. More than 1000 patients in case series, at least 2 case-control studies, and a preliminary report from the ongoing clinical trial at M.D. Anderson in Texas had all failed to detect an increase in treated women. Therefore the almost automatic reaction to the Swedish trial, as articulated in the accompanying editorial, is that the previous data reflect biases, such as selection of low-risk women for treatment (in my view, a very reasonable criticism), restaging of women at entry that removes women with early recurrences, and selective publication of studies reporting a protective effect (how in the world would we ever know if other studies were performed and not publicized?). But isn't it time that we apply the same critical approach to randomized trials? Didn't our experience with the Women's Health Initiative teach us this? Therefore, let's consider

VOLUME 20 • NUMBER 12 • APRIL 2004 • PAGES 89-96

some criticisms of HABITS.

HABITS was not the only clinical trial organized in Sweden to study hormone therapy in breast cancer survivors. A similar trial was ongoing in Stockholm. At the time of the safety analysis, the relative hazard in Stockholm was 0.82 (CI = 0.35-1.9), compared to 3.3 (CI = 1.5-7.4) in HABITS. The HABITS report pointed out that the difference between the studies represented a statistically significant heterogeneity (the difference between the 2 trials was statistically significant), and it was a puzzle why the trials differed. Unfortunately, because of the decision regarding the HABITS trial, the Stockholm trial was also canceled, because of anticipated difficulties with recruitment and compliance. Indeed, the reason for analyzing both trials together is that a decision was made in 2002 to pool the data because of slow recruitment. Does the difference invalidate the HABITS' conclusion? That's a difficult question to answer.

HABITS was not a double-blinded, placebo-controlled trial. Women in the treated group were openly compared to the nonhormone treated group. The treated group (174 women) consisted of estrogen only (21%), sequential estrogen-progestin (26%), and continuous combined estrogen-progestin (46%). Comparison of regimens did not yield significant differences. However, 11% of the treated group used other treatments, including tibolone, even though it was supposed to be excluded. In the comparison group (171 women), 18% of the women were treated with hormone therapy. From the reported analysis, the effect of this variation and crossover cannot be ascertained.

In the treated group, 21 of the 26 women with recurrent disease were diagnosed while on the planned 2-year treatment. Did this rapid appearance of recurrent disease (median follow-up of 2.1 years) reflect an impact of hormone treatment on pre-existing disease, a bias that could have been present because of the failure to re-stage disease on entry to the study?

The HABITS report indicated that the characteristics of the 2 groups did not influence the results with the possible exception of hormone receptor status. The two groups did differ, with the following characteristics more prevalent in the hormone-treated group: positive nodes, positive hormone receptors, unknown hormone receptor status, and fewer mastectomies. A statistical analysis of these differences was not provided. The relative hazard comparing the hormone-treated women and the comparison women in each of the subgroups (grouped according to baseline characteristics) was presented, and a significant increase was present in the following subgroups: positive hormone receptors, no tamoxifen, and hormone therapy before diagnosis. The problem is that the confidence intervals were very wide because of small numbers, and the report acknowledged the very low precision. Is it possible that these differences represented the greater prevalence in the treated group of the previously noted baseline characteristics?

Hopefully the report from HABITS will not cause cancelation of the other ongoing clinical trials investigating the use of hormone therapy in breast cancer survivors. It seems to me that there are too many questions and problems with the HABITS study to consider it definitive. Having said that, the report certainly makes it more difficult for clinicians and breast cancer patients to accept the unknown risks and use hormone therapy. I will continue to support patients with whatever decision they make once they are fully informed regarding the accumulated data. ■

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina Petrone.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421
Editorial E-Mail: robert.kimball@thomson.com
Customer Service E-Mail: customerservice@ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $249
(Resident/Student rate: $125).
Multiple Copies
1-9 additional copies: $224 each; 10 or more copies: $199 each
Canada
Add GST and $30 shipping
Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.

Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2004. This volume has been approved for up to 25 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Robert Kimball**, Assistant Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genentech, GlaxoSmithKline, Atairigen, and the National Cancer Institute. Dr. Hobbins reports no relationships related to this field of study.

Cervical Adenocarcinoma and Squamous Cell Carcinoma Incidence Trends Among White and Black Women in the United States

ABSTRACT & COMMENTARY

Synopsis: *Changes in screening, endocervical sampling, nomenclature, and improvements in treatment likely explain the increased in situ cervical SCC incidence in white and black women. Increasing AIS incidence over the past 20 years in white women has not yet translated into a decrease in invasive AC incidence.*

Source: Wang S, et al. *Cancer*. 2004;100:1035-1044.

It is widely recognized that cervix cancer incidence rates have declined greatly in the United States following introduction of the Papanicolaou smear. However little is known about these rates among different histological subtypes. Wang and colleagues from the National Cancer Institute analyzed the Surveillance, Epidemiology, and End Results (SEER) database to evaluate this trend for a 25-year period, ending in the year 2000. The SEER Program collects data from 9 geographically distinct population-based cancer registries and is available for public analysis. Incidence rates by histologic subtype, namely adenocarcinoma and squamous cell carcinoma, race, age and disease stage were computed and analyzed for trends. For both races, overall incidence of invasive squamous cell carcinoma declined over time and the majority of tumors currently detected are carcinoma in situ and localized cancers. Most striking was an increase in the incidence of squamous cell in-situ disease reported over the final decade of analysis. Adenocarcinoma in situ rates among both races has increased and adenocarcinoma incidence has increased among young white women. In black women, invasive adenocarcinoma increases with age. Wang and colleagues conclude that changes in screening, endocervical sampling, nomenclature and improvements in treatment likely explain the increased squamous cell carcinoma in situ and decreased invasive squamous cell carcinoma incidence rates among both races. However, unlike this histology, the increased incidence of adenocarcinoma in situ diagnosis has not yet translated into a decreased incidence of invasive adenocarcinoma. The relationship of adenocarcinoma incidence and age among black women may reflect lack of effective screening or differential disease etiology.

COMMENT BY ROBERT L. COLEMAN, MD

One of the greatest successes in cancer prevention in the United States is undoubtedly the Pap smear. Introduced to a speculative audience by Dr. Papanicolaou in the 1940s, the Pap smear is now ubiquitously available, the focus of National screening programs (such as the National Breast and Cervical Cancer Early Detection Program) and individually responsible for a dramatic decrease in disease-specific mortality witnessed over the last 60 years. In many ways it is the ideal screening tool for a disease, which, by its nature, is "screen-able." Yet nearly half of new cervical cancer cases occur in women either previously unscreened or infrequently screened.

In this study, Wang et al accessed the SEER Program to evaluate recent trends in the diagnosis of "significant" lesions (*in situ*, localized, regional and advanced) by histology (squamous cell vs adenocarcinoma), race (white and black), and age. This database represents about 10% of the US population and has been particularly useful in providing insight into population-based cancer trends. While inconsistencies in data reporting and lack of precise parity with individual cancer staging criteria are limiting, the large number of available patients allows analysis of otherwise inevaluable trends and rare diagnoses. In the current study, the strength of the database is used to evaluate cancer trends of the uncommon adenocarcinoma histology and its incidence among different races and ages. What is of particular interest is the relationship of *in situ* disease and cancer. It would seem logical that if our efforts in screening were successful, we should identify more preinvasive conditions resulting in declining rates of cancer. This "stage" migration effect is clearly confirmed among both races for squamous lesions. Unfortunately, the same has not yet been realized for adenocarcinoma lesions, particularly among black women. In recent years, cytopathologists and investigators have not only become more savvy in making these diagnoses on Pap smears but also have modified the criteria of reporting these lesions so as to not confuse them with their squamous counterparts. However, many studies continue to report not only increasing adenocarcinoma to squamous cell carcinoma ratios but also real increases in new adenocarcinoma diagnoses. In the current study, adenocarcinoma incidence is increasing, particularly among young (25 to 34 year-old) white women and in all age groups of black women. Interestingly, incidence rates of invasive adenocarcinoma plateau at about age 35 for white women yet continue to increase in blacks, being highest in the 75 and older cohort. If screening practices are equivalent, why is this effect being seen?

The answer is not immediately available in the cur-

rent report. However, some hypotheses may be drawn in evaluating known risk factors for invasive adenocarcinoma and balancing these against population trends over the study time interval. Nulliparity and obesity have been associated with cervical adenocarcinoma risk and both have increased in recent years. Although a hormone effect from endogenous obesity may influence incidence, it has been hypothesized that just the occurrence of obesity may interfere with effective population-based screening and complicating detection. Still, the age-effect seen between the races suggests an etiological factor not heretofore identified. HPV-18 is most often HPV subtype associated invasive cervix adenocarcinoma. It is unknown if prevalence rates have altered over the last 25 years or whether the cofactors previously mentioned interact with this viral infection to effect this observation. More mechanistic investigation is needed.

In the big picture, significant progress is being made in the United States thanks to the tireless efforts of our healthcare providers. More needs to be done to ensure that all women are appropriately screened and managed for pre-invasive disease. However, the worldwide burden problem cannot be overlooked and it is hoped an effective model can be enacted in those high-risk populations where resources are more limited. ■

Suggested Reading

1. Altekruse SF, et al. *Am J Obstet Gynecol*. 2003; 188:657-663.
2. Hiatt RA, et al. *J Natl Cancer Inst*. 2002;94:1837-1846.
3. Lacey JV Jr, et al. *Cancer*. 2003;98:814-821.
4. Smith HO, et al. *Gynecol Oncol*. 2000;78:97-105.
5. Solomon D, et al. *JAMA*. 2002;287:2114-2119.

BRCA Germline Mutations in Jewish Women with Uterine Serous Papillary Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *The loss of heterozygosity in the tumor tissue of carriers coupled with the high frequency of patient and family history of breast and ovarian malignancies suggest that USPC might be part of the manifestation of familial breast-ovarian cancer in Ashkenazi Jews.*

Source: Lavie O, et al. *Gynecol Oncol*. 2004;92: 521-524.

Lavie and colleagues previously described a possible link between germline mutation in the BRCA genes and the occurrence of the uncommon, but aggressive uterine papillary serous carcinoma (UPSC). The purpose of the current study was to expand the investigation, evaluate the incidence of personal breast cancer and family history and to determine if tumor tissues harbored similar genetic mutations as the germline. To do this, they retrospectively identified 27 women consecutively diagnosed with UPSC over a 2½ year interval at 3 institutions. Identified cases were interviewed for family history and given genetic counseling. Peripheral blood was taken for genomic DNA analysis and paraffin-embedded tissue was harvested for loss of heterozygosity analysis (LOH). Mutational analysis was conducted for one of the 3 well-characterized founder mutations for women of Ashkenazi decent. Overall, 4 of 20 (20%) Ashkenazi and 0 of 7 non-Ashkenazi women were identified with a founder mutation. Personal history of breast cancer was identified in 7 (35%). Family history of breast (65%), and ovarian (20%) cancer were common. The diagnosis of breast cancer preceded uterine cancer by 11.5 years. LOH analysis identified loss of the wild-type allele in 3 of the 4 BRCA1 mutations. Lavie et al concluded that Ashkenazi women diagnosed with UPSC have a high incidence of BRCA founder mutations. LOH analysis coupled with the significant family history reported in this cohort suggested that UPSC might be a clinical manifestation of the familial breast-ovarian cancer syndrome in Ashkenazi women.

COMMENT BY ROBERT L. COLEMAN, MD

There is little underestimation of the clinical significance conveyed in identifying a familial cancer syndrome for a particular patient. Once hidden from public record for fear of "genetic discrimination," the knowledge of an inherited predisposition has allowed physicians and patients to not only critically assess cancer risk but also evaluate potential preventive strategies that could impact that risk over time. As more sophisticated models assessing risk are developed and acceptance for available testing is increased, greater precision in counseling can be realized. A necessary component of this counseling is understanding how to interpret "risk" estimates and where this risk may manifest.

As Obstetrician/Gynecologists, our closest clinical experience in this regard comes in the care of women with mutation in the BRCA family of genes. The familial breast-ovarian cancer syndrome, most commonly characterized by an increase in lifetime risk of both breast and ovarian cancer, is infrequently diagnosed (about 10% of primary ovarian cancers), yet it is the subject of intense investigation. Important information from

this work has identified, for instance, that a wide range of variable penetrance exists between different families; specific cohorts are at risk because of their ethnicity (Ashkenazi Jews); and intervention strategies such as oral contraceptives and prophylactic surgery (salpingoophorectomy, mastectomy) appear to reduce the risk of cancer at both sites. New developments continually shape our understanding of the disease process and with this knowledge, new recommendations.

Lavie et al raise another consideration in the current article. They reasoned that since UPSC and serous epithelial ovarian cancer have similar morphology and clinical behavior and since ovarian cancer in Ashkenazi Jewish women is associated with the high background incidence of BRCA founder mutations, there might be an association between UPSC occurrence and BRCA mutation. Although only 4 women with mutations were identified in the cohort of Israeli Ashkenazi Jews, the 20% incidence is dramatically different than the Ashkenazi population risk in general (2%) and surprising similar to the incidence of mutation in their women diagnosed with either ovarian (30%) or breast (10%) cancer. Loss of heterozygosity analysis suggests the germline mutation was potentially causally related to their cancer occurrence. The clinical implication of documenting UPSC as a potential clinical manifestation of the cancer syndrome lies in screening and prophylactic surgery. That is, if the disease is a future risk for women identified with or at risk for mutation of BRCA, should our recommendation for risk reduction include hysterectomy?

To answer this question appropriately, more clinical data are needed. The association documented in the current report is far from congruent with other investigations. For instance, in the largest series of UPSC patients for whom BRCA analysis was conducted, no BRCA1 or BRCA2 mutations were found; in a smaller series of UPSC tumors by Goldman et al, 3 of 9 cases were identified with BRCA2 mutations, whereas in the current report, only mutations in BRCA1 were found. Nonetheless, management of women undergoing prophylactic surgery for known or suspected BRCA mutation is more complex when uterus is left *in situ*. It has been documented that along with ovarian cancer, the relative risk for tubal malignancy is significantly elevated. Although most tubal cancers are distally situated, removal of the entire tubal segment cannot be completely accomplished by salpingoophorectomy—a theoretical consideration. In addition, newly castrated young women will likely choose hormone therapy for symptomatic indications. Generally, this medication is prescribed as a combination in those with a uterus to offset the risk for endometrial cancer. However, the associated risks for subsequent breast cancer with combination hormone replacement therapy have been suggested in recent reports from the Women's Health Initiative trials.

Nonetheless, if clear association of UPSC as a clinical manifestation of the familial syndrome can be made, it should prompt us to expand our discussions with these high-risk women and potentially modify our recommendations for prophylactic surgery. At the end of the day, provocative data, as that raised by Lavie et al, need to be critically evaluated. The recommendation for universal hysterectomy in affected patients wanting prophylactic surgery is premature. Data from additional analytical trials will help to further refine this recommendation, hopefully, improving the lives of women identified with familial cancer risk. ■

Suggested Reading

1. Goshen R, et al. *Gynecol Oncol*. 2000;79:477-481.
2. Grann VR, et al. *J Clin Oncol*. 2002;20:2520-2529.
3. Rossouw JE, et al. *JAMA*. 2002;288:321-333.
4. Rebbeck TR, et al. *N Engl J Med.* 2002;346:1616-1622.
5. Goldman NA, et al. *ASCO Proc.* 2002;21:221a.

Microchimerism: An Investigative Frontier in Autoimmunity and Transplantation

ABSTRACT & COMMENTARY

Synopsis: *Maternal-to-fetal and fetal-to-maternal microchimerism likely play a role in the development of several autoimmune conditions and may modulate the severity of host-vs-graft disease after transplantation.*

Source: Adams KM, Nelson JL. *JAMA*. 2004;291(9): 1127-1131.

In this article, Adams and Nelson integrate results from several disparate fields to advance the concept that autoimmune conditions resemble host vs graft disease and that the "graft" in many cases may be fetal or maternal cells that lodge in the "host," namely the mother or fetus, respectively. Technically, microchimerism refers to a small population of cells or DNA in one individual that derives from another genetically distinct individual. Cell traffic between mother and

fetus during pregnancy is common and has been demonstrated to lead to long-term persistence of fetal cells in the mother (fetal microchimerism) and maternal cells in the progeny (maternal microchimerism). In this context, long-term means decades or forever. Apparently, microchimerism may follow ectopic pregnancy, miscarriage, and abortion as well as term pregnancy. Potentially, during multiple gestation, there may be fetus-to-fetus transmission.

Microchimerism may also result from blood or other transfusions. Autoimmune conditions that have been linked to microchimerism include scleroderma, thyroiditis, primary biliary cirrhosis, Sjögren syndrome, adult and neonatal lupus, and dermatomyositis. To enhance detection of microchimerism, studies initially used women who had delivered sons to demonstrate the persistence of cells with XY chromosomal status lodged in maternal tissues. Using these techniques, fetal cells were found in the skin of women with scleroderma. Not unexpectedly, HLA genes appear to be involved. For instance, prior birth of a child that is identical to the mother at the HLA-DR locus increases the risk of scleroderma by 7-fold. The extent (dose) of microchimerism may also gate the likelihood of developing an autoimmune condition or modulate its severity. Immune responses could be amplified by indirect antigen presentation from "graft cells" or by T-cells released from the "graft" into the host circulation. Microchimerism of maternal cells in the fetus may have different effects than vice versa, because the maternal cells are present while the fetal immune system is still developing. This is a new field, so long-term prospective data are not available. Adams and Nelson conclude that fetal and maternal microchimerism can have adverse, neutral, or beneficial effects on the host, depending on many factors, including HLA subtypes and fetal-maternal HLA concordance.

COMMENT BY SARAH L. BERGA, MD

This article is particularly germane to physicians who care for women as it may help to explain sex-based differences in disease presentation or incidence. It has long been recognized that there is a female preponderance in autoimmune conditions. Microchimerism provides a putative reason for why women, especially those who have had several pregnancies, might have a higher incidence of immune dysregulation than men. It is not yet clear whether reproductive events lead to a greater risk of maternal or fetal microchimerism, but advances in molecular detection will likely permit the conduct of more detailed and longitudinal studies. Being able to rapidly and accurately detect microchimerism raises the hope that we can then implement therapies to control its negative consequences. For instance, knowledge about the effect of hormone perturbations, such as those that accompany puberty or perimenopause, upon microchimeric rests may explain the timing of the presentation of conditions such as lupus or fibromyalgia. This study raises many questions. Would postmenopausal hormone use exacerbate or ameliorate latent graft vs host reactions? What is the effect of hormonal contraceptives?

Since microchimerism appears to be a common consequence of pregnancy, one wonders if there are ways to minimize the likelihood of this bidirectional transfer. For instance, does fetal surgery, umbilical vein sampling, version, or even amniocentesis increase the likelihood of microchimerism? Is the likelihood greater after cesarean section as opposed to vaginal delivery? As we improve our ability to perform pre-implantation genetic diagnosis, might we want to select against replacing embryos that are identical to the mother at the HLA-D locus for both maternal and fetal reasons? There is clearly much to learn, but until a few years ago, we never knew that we could or should address these questions.

As our techniques improve, we might be able to define the fetal and maternal consequences of pregnancy in women with established maternal microchimerism (ie, when the mother harbors cells from her mother dating to her fetal life) or in women who becomes engrafted during a preceding pregnancy. If immune activation or tolerance plays a role in recurrent miscarriage, would this risk increase or decrease with increasing microchimeric burden or activity? Further, one would expect that we might be able to determine if endometriosis is more or less common in women with microchimerism or if the HLA-D locus of the engrafted cells plays a role in who does and does not get endometriosis.

The main focus of this article was on the consequences of microchimerism for elucidating why rejection does or does not occur in individuals with relatively appropriately matched transplants. Given the likelihood that there will be increasing use of transplantation, it will clearly be important to know what gates rejection. In the article, the notion is advanced that immune tolerance may be enhanced by promoting microchimerism via repeated blood transfusions. This is reminiscent of the use of paternal cells to induce immune tolerance in women with recurrent miscarriage. Perhaps more rational approaches can be devised if we can accurately determine who is a candidate for immune modulation. In short, this is a noteworthy article because it brings to our attention an area of

immunology likely to play an increasing role in understanding and treating women's health conditions ■

Abdominal and Vaginal Colpopexy Comparable for Vault Prolapse

ABSTRACT AND COMMENTARY

Synopsis: *Both surgical approaches are highly effective in the management of vaginal vault prolapse.*

Source: Maher CF, et al. *Am J Obstet Gynecol*. 2004; 190:20-26.

Ninety-five patients with vaginal vault prolapse were randomly assigned to having either an abdominal sacral colpopexy with Prolene mesh or unilateral sacrospinous colpopexy. All patients in both groups with stress incontinence also had Burch colposuspension. Follow-up for up to 5 years after surgery revealed both subjective success for the abdominal (94%) and vaginal approaches (91%) and objective success (76% and 69% respectively). The abdominal approach was associated with longer operating room time, higher cost, and longer convalescence.

■ **COMMENT BY FRANK W. LING, MD**

First, there's the article itself. This well-designed Australian study addresses an increasingly common condition, post-hysterectomy vault prolapse. With an aging patient population, additional risk factors of years since hysterectomy and hysterectomy for genital prolapse are of even greater import. Extensive baseline data allow for thorough comparison of preoperative and postoperative conditions. A patient who has no prolapse symptoms is considered a "subjective success." Objective "success" is defined as no prolapse beyond the halfway point of the vagina during Valsalva. Trends in the data bring Maher and colleagues to suggest that the abdominal approach may be preferable if the prolapse is predominately anterior while the vaginal surgical approach may be preferred for posterior prolapse. In either approach the procedure is likely to cure any pre-operative urinary voiding dysfunction while having little effect on bowel function.

Second, there's your practice. You aren't going to do enough of these cases to do your own randomized study. By the same token, you are likely to already prefer one procedure over the other. The perspective that you should adopt is that of thorough consideration at several critical points:

a. At the time of any hysterectomy, but particularly when prolapse is present, make sure that support to the vault is provided when needed;
b. When caring for a patient after hysterectomy, watch for signs and symptoms of prolapse;
c. When vault prolapse is found, pursue non-surgical options such as Kegel exercises and pessary placement initially;
d. As prolapse is being diagnosed and treated, assess urinary function completely;
e. When selecting a surgical approach for prolapse, factor in the findings of this study as well as your own surgical experiences.

Special Feature

What is the Best Way to Monitor Maternal Temperature in Labor?

By John C. Hobbins, MD

To answer the above question a team of British investigators (Banerjee S, et al. *Obstet Gynecol*. 2004;103:287-293) inserted an intrauterine temperature sensor in 18 laboring patients with epidural anesthesia at the time they were inserting intrauterine pressure catheters. These patients then were monitored with periodic oral thermometer sampling, continuous skin temp assessment (taped to the inner thigh) and the commonly used ear canal temperature assessments.

Banerjee et al Found:

1. Intrauterine temperatures rose on average throughout labor (average at a rate of 0.04ºC per hour);
2. The average intrauterine temperature was 38.1ºC in this group, compared with previous studies in which temps varied between 36º and 37º C in patients without epidural.
3. Most important, the oral temperature was the most consistent predictor of intrauterine temperature, undershooting on average by 0.8ºC.

It is clear from this study that oral temperatures reasonably reflect intrauterine temperature (with a sensitivity of more than 80% and a specificity of 96%) once one adds 0.8ºC to the reading. The study also shows that skin

temperature assessments, theoretically representing vasodilation and ear canal methods to reflect tympanic membrane temperature, are poor indicators of maternal core temperature.

That said—how important is it to accurately predict the intrauterine temperature? Data from recent investigation in humans and in personal models suggest the following:

1. fetal core temperature is about 0.5ºC higher than intrauterine temperature;
2. an increase in fetal brain temperature even in the absence of infection has an additive effect in brain damage from fetal hypoxia/ischemia;
3. increases in maternal temperature, grossly reflecting many etiologies, is associated with many adverse pregnancy outcomes;
4. epidural does seem to elevated maternal core temperature.

So from the above "true and maybe related," it seems reasonable to keep track of maternal temperature at frequent intervals, and if one excludes intrauterine temperature assessments as being invasive and maternal rectal thermometer assessment as being intrusive (as one patient survey has shown), then, let's say, hourly oral temp taking could suffice.

Last, one of the earliest clues of increasing maternal core temperature in labor is a fetal tachycardia. Elevation in baseline fetal heart rate is generally not an indirect reflection of fetal infection but simply represents how poorly equipped the fetus is to dissipate heat without the usual mechanisms that infants possess. However, heat by itself may represent potential trouble for the fetus and should be monitored carefully. ■

Suggested Reading

1. Wass CT, et al. *Anesthesiology*. 1995;83:325-335.
2. Dietrich WD, et al. *Stroke*. 1990;21:1318-1325.
3. Lieberman E, et al. *Pediatrics*. 2000;105:8-13.
4. Lieberman E, et al. *Pediatrics*. 2000;106:983-988.

CME Questions

5. **All of the following are factors contributing to the incidence of post-hysterectomy vaginal vault prolapse *except*:**
   a. aging patient population.
   b. Yyears since hysterectomy.
   c. Hhysterectomy for prolapse.
   d. concurrent urinary incontinence.

6. **The following statements are true regarding the Swedish HABITS study *except*:**
   a. The HABITS study was a randomized, blinded study.
   b. The HABITS study was a randomized, open, comparison study.
   c. Hormonal and non-hormonal treatment of the women in the HABITS study was random and varied.
   d. The two groups were not identical in tumor characteristics (receptor status, positive nodes, mastectomies).

7. **Microchimerism has been implicated in the pathogenesis of all of the following *except*:**
   a. thyroiditis.
   b. scleroderma.
   c. osteoporosis.
   d. lupus.
   e. rejection of kidney transplants.

Answers: 5 (d); 6 (a); 7 (c)