AMERICAN HEALTH CONSULTANTS®

Providing Evidence-based Clinical Information for 18 Years

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Vaginal Birth After Cesarean

ABSTRACT & COMMENTARY

In the july 5, 2001, issue of the *New England Journal of Medicine*, the lead article was entitled, "The Risk of Uterine Rupture during Labor among women with a Prior Cesarean Delivery." Lydon-Rochelle and colleagues retrospectively analyzed data from the Washington state birth-events database from 1987 to 1996. Information was available on 20,095 patients who had had cesarean delivery and then delivered another child vaginally during this study period.

Uterine rupture occurred in 1.6 per 1000 patients who had repeat cesarean delivery without labor and in 5.2 per 1000 of those who had spontaneous onset of labor. If labor was induced with oxytocin, the rupture rate was 7.7 per 1000 and 24.5 per 1000 when a prostaglandin (PG) preparation was used. Since misoprostol (PGE1) was introduced to Washington state the year the study was completed, it is likely that few of the PG-induced patients actually got this agent.

The relative risk (RR) of uterine rupture for repeat cesarean section without labor was 3.3 (confidence interval [CI] 1.8-6.0), induction of labor without PGE was 4.9 (CI, 2.4-9.7), and labor with prostaglandins was 15.6 (CI, 8.1-30.0). (Lydon-Rochelle M, et al. *N Engl J Med.* 2001;345:3-8).

COMMENT BY JOHN C. HOBBINS, MD

The national cesarean delivery rate peaked in 1989 to 25%, and fell to 21% in 1996 and has since remained the same. Although there were many contributors to this downward trend, such as monitoring through peer review, liberalization of second-stage progress requirements, and perhaps, a more active management of labor, the emphasis on the option of vaginal birth after cesarean delivery (VBAC) had to have played a major role.

The popularity of VBAC was predicated on the excellent safety record generated during many early trials. Now that there is evidence emerging that VBAC may not be a good idea for everyone. Studies have surfaced, like the *New England Journal of Medicine* report above, that have shown a greater risk of uterine rupture when

Volume 18 • Number 7 • November 2001 • Pages 49-56

INSIDE

PGs are used for induction. In the *New England Journal of Medicine* article, it was unclear which type of PG was used (intravaginal PGE2 suppositories or intracervical PGE2 gel), but the timing of the study precludes PGE1 as being a contributor to uterine rupture in this study. However, there are a few recent reports that suggest that misoprostol has an even higher rate of uterine rupture in VBACs, and this has caused the American College of Obstetrics and Gynecology to advise against its use in VBACs.

The original rationale for the use of various PG derivatives was not necessarily to induce labor, but to ripen the cervix either through generating mini-contractions or to "soften" the cervix through an effect on collagen and elastin. What seems to have been overlooked was the possibility that while softening the cervix, one might also be softening the uterine scar, and PGE1 might be the best scar softener around.

On the other hand, PG may not be the culprit here. By implication, PG derivatives are used predominantly when the cervix is unripe, and the increased risk of rupture may well be more related to the process of trying to initiate an induction in a woman who has a scar in her uterus and a cervix that is unready for labor. This could also explain the difference in uterine rupture in the above study between patients in spontaneous labor and those induced with oxytocin.

It is important to make a clear distinction between induction and augmentation. By definition, the latter is applied to those already in spontaneous labor—those who have passed through some natural early physiologic processes but who need a little help with contractions. Naiden and Deshpande recently published 10 years of experience in which an active management of labor protocol (with liberal use of oxytocin augmentation) was used successfully to diminish the overall cesarean section rate from 16.6% to 10.9%, and the repeat cesarean section rate from 7.3% to 3.8%. During this time, there were 2 uterine ruptures in the 1200 successful VBACs. Neonatal mortality did not change during the study period. So, undoubtedly, judicious use of oxytocin, especially for augmentation, should not be interdicted in VBACs.

On a pragmatic note, whether we like it or not, almost everything we do today is scrutinized according to its cost-effectiveness. In an ambitious study, Chung and colleagues subjected data from 22 years worth of VBAC studies in the literature to mathematical modeling in order to determine its cost-effectiveness compared with outright repeat cesarean section. When taking into account the cost of the cesarean delivery vs. vaginal delivery, and folding in the expense of the maternal and neonatal complications, Chung et al found that the bottom line was very dependent upon the success of the endeavor. VBAC was clearly cost-effective only when the success rate exceeded 75%.

Is there a way to identify patients with uterine scars who are at the greatest risk of rupture? In a study from Japan, Gotoh and associates attempted to predict uterine rupture by evaluating the thickness of the scar with transabdominal and transvaginal ultrasound. They found that the magic number below which there was a substantial risk of rupture was 2 mm. If the thinnest portion of the uterus in the neighborhood of the scar exceeded 2.9 mm, the risk of rupture was negligible.

Our initial excitement about the study has been dampened somewhat by our difficulty in obtaining adequate transvaginal images of the uterine scar when enough urine is in the patient's bladder to precisely measure wall thickness. Also, in 1 case of a uterine "window" and another case of frank rupture, the wall thickness exceeded 2.9 mm just prior to delivery.

There are many disincentives for the obstetrician to embark upon VBAC, such as risk of uterine rupture, the

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

VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSOCIATE MANAGING EDITOR: Neill Larmore.
SENIOR COPY EDITOR: Robert Kimball.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

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

Back issues: $37. Two to nine additional copies, $197 each; 10 or more additional copies, $175 each. 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.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

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

Subscription Prices

United States
$269 per year
(Resident/Student rate: $99).
Multiple Copies
1-9 additional copies: $197 each; 10 or more copies: $175 each
Canada
Add GST and $30 shipping
Elsewhere
Add $30 shipping

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational 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.
This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2001. This volume has been approved for up to 20 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

Questions & Comments

Please call **Robin Mason,** Managing Editor, at (404) 262-5517 or **Robert Kimball**, Senior Copy 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, Parke-Davis, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Parke-Davis, 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, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Noller and Dr. Hobbins report no relationships related to this field of study.

necessity of onsite supervision, and the questionable cost-effectiveness of the venture. However, perhaps the greatest deterrent is the potential for a bad outcome to wind up in the courts. So, should VBAC be abandoned? No! There is solid evidence that while VBAC may not be for everyone, it is safe and effective for some, especially since many patients are highly motivated to choose this option. The ideal patient would be one who has an excellent chance of succeeding and in whom a minimum of medication and intervention would be needed. For example, this would be a patient who has entered into spontaneous labor or whose cervix is easily inducible with oxytocin (Bishop score greater than 4). The estimated fetal weight should be reasonable and the patient should make excellent progress through labor.

Most importantly, before embarking on VBAC, the patient must be carefully counseled about its risks, benefits, and expectations of success. The stark wording of some consent forms, such as those drafted by malpractice insurers, can make some patients wonder if *pregnancy* is a good idea. Therefore, verbal embellishment is essential in the consent process. ❖

Suggested Reading

1. Wing DA, et al. *Obstet Gynecol*. 1998;91:828-830.
2. Induction of labor with misoprostol. ACOG Committee Opinion Number 228. Presented at meeting of the American College of Obstetrics and Gynecology; November 1999; Washington, DC.
3. Naiden J, Deshpande P. *Am J Obstet Gynecol*. 2001; 184:1535-1543.
4. Chung A, et al. *Obstet Gynecol*. 2001;97:932-941.
5. Gotoh H, et al. *Obstet Gynecol*. 2000;95:596-600.

Cervical Cancer Screening by Simple Visual Inspection After Acetic Acid

ABSTRACT & COMMENTARY

Synopsis: *In developing countries, visual inspection of the cervix after acetic acid application may prove to be a useful screening test for neoplasia.*

Source: Belinson JL, et al. *Obstet Gynecol*. 2001;98: 441-447.

In many areas of the world, cervical cancer remains a common malignancy of adult women. Unfortunately, many developing countries cannot afford the cost of cytology screening programs, colposcopic triage, and subsequent therapy for preinvasive disease. One strategy that is being developed for cancer screening in these areas is the visual inspection of the uterine cervix after the application of acetic acid. Several preliminary articles have suggested that the technique may have sufficient sensitivity and specificity to be useful.

This study was performed in the Shanxi Province of China in 1997. A total of 1997 women were screened. All had a cervical speculum placed, 5% acetic acid applied to the cervix, and visual inspection of the cervix performed 1 minute later. The visual inspection results were reported as normal, low-grade, high-grade, or cancer. Following this inspection, physicians who had not performed the visual inspection performed a colposcopic evaluation. Abnormal areas were biopsied as well as at least 1 biopsy from each quadrant of the cervix, and an endocervical curettage.

As would be expected, most women in the study had normal visual inspection and normal biopsies. Of these, 552 (28%) had visual abnormalities; 27 were visually either high-grade lesions or cancer.

The biopsies identified 86 women with CIN II or greater lesions. When all women with any visual abnormality (low-grade, high-grade, or cancer) were considered as a group, 61 of 86 CIN II or greater lesions were identified. The positive predictive value in these 552 women with any abnormality was 11%.

Belinson and associates suggest that visual inspection of the cervix may be a legitimate technique for screening in developing countries as it requires very few supplies and low cost. The training is simple. Diagnosis and treatment can be achieved at the time of a single visit.

COMMENT BY KENNETH L. NOLLER, MD

The reason I chose this article was to make our readers aware of the fact that visual inspection of the cervix after the application of acetic acid is becoming an accepted technique for cervical cancer screening in developing countries. My first introduction to the technique was at an international conference on cervical cancer screening that I attended several years ago. The conference was very enlightening and opened my eyes to an entirely different way of thinking about such screening. In the United States, as we all know, virtually nothing less than complete identification of every significant cervical neoplasia is required. However, such precision comes at quite a price. When one considers the cost of a Pap smear and office visit (even without considering such things as lost time from work, transportation, and child care), an annual Pap smear may easily cost $100. In developing countries, Pap smear screening costs must

be held to a minimum, and several developing countries have reported total screening costs of less than $0.25 per individual. While these inexpensive techniques (such as visual inspection) do not identify all significant disease, they are "good enough" to identify most cases and should ultimately be shown to decrease the incidence of cervical cancer.

I do have some concerns with some of the results and conclusions in this paper. While visual inspection was able to identify 71% of the biopsy-positive cases of CIN II or greater, this was only accomplished when all 552 women with low-grade or more changes were biopsied. That is, 28% of the screened population had some changes that would require either referral for colposcopy, random biopsy, or immediate treatment. If all were treated, about 90% would have no disease or minimal disease. Additionally, visual inspection only suspected invasive cancer in 6 women, 3 of whom had the disease. Three other patients were in the high-grade group and 2 hidden among those with low-grade changes. Four of the 12 cases would have been missed.

I strongly suspect that visual inspection will ultimately become a common technique for the detection of cervical neoplasia in developing countries. While a few women with significant lesions will be missed, the majority should be identified. In many parts of the world, this may be acceptable—at least at the present time. ❖

Do Third-Generation Oral Contraceptives Have a Higher Risk of Venous Thrombosis?

ABSTRACTS & COMMENTARY

Synopsis: *There continues to be confusion over whether third-generation oral contraceptives are associated with a higher risk of venous thromboembolism compared with older products.*

Sources: Kemmeren JM, et al. *BMJ*. 2001;323:131; Jick H, et al. *BMJ*. 2001;321:1190-1195.

Kemmeren and associates from the university Medical Centre in Utrecht in The Netherlands performed a meta-analysis of the studies assessing the risk of venous thromboembolism (VTE) associated with oral contraceptives (OCs). Of 114 identified studies, 13 were accepted for inclusion. The analysis concluded that the odds ratio (OR) for the risk of VTE was 1.7 (confidence interval [CI], 1.4-2.0) comparing users of desogestrel- and gestodene-containing OCs with users of levonorgestrel-containing products. Among first-time users, the OR was 3.1 (CI, 2.0-4.6) comparing the newer products to the older OCs.

Jick and associates from Boston University used the General Practice Research Database from general practices in the United Kingdom to perform additional case-control and cohort studies of the risk of VTE in users of OCs. The analyses compared users of levonorgestrel-containing OCs with users of desogestrel- and gestodene-containing OCs (so-called third-generation OCs). Because use of third-generation OCs dramatically declined after the reports in 1995-1996 that these products had higher risks of venous thrombosis (VT), Jick et al assessed the incidence of VTE in a cohort population before and after the "pill scare." In both periods of time, the risk of VTE was twice as great associated with third-generation products compared with pills containing levonorgestrel. Jick et al concluded that because there was no change before and after the pill scare, the difference reflects an inherent difference between products. In the case-control analysis, each case was matched with women of the same age who went to the same clinician and were using pills at the same time. Adjustments were made for body mass index, smoking, duration of pill use, and switching of pills. The OR for VTE in third-generation pill users compared with levonorgestrel users was 2.3 (CI, 1.3-3.9). In contrast to previous studies, smoking was found to be associated with a significant increased risk of VTE.

COMMENT BY LEON SPEROFF, MD

This story goes back and forth. The original reports uniformly concluded that OCs containing gestodene or desogestrel had twice the risk of VTE compared with levonorgestrel-containing products.[1-5] These results were immediately challenged. The studies were believed to reflect 2 consistent problems: preferential prescribing and the healthy user effect. Clinicians were swayed by advertising claims and believing the new products to be safer more often than prescribed third-generation products to new users and women perceived to be at higher risk. Individuals who do well with a product tend to remain with that product; therefore, individuals on an older product will be relatively healthy and free of side effects. Thus, comparing users of older and newer products involves 2 groups of women that are not identical.

Studies accounted for the above criticisms by focusing on first-time users and adjusting for duration of use. These studies failed to demonstrate a difference between

third-generation products and levonorgestrel-containing OCs.[6-9] Nevertheless, the meta-analysis summarized above reported the difference between third-generation and older products was still present in first-time users. They fail to report a clear analysis of the effect of correcting for duration of use. Preferential prescribing is dismissed by referring to "2 studies" (both from the same investigators) that, in fact, analyzed the effect of referral bias not preferential prescribing.[10,11] I am not impressed with the quality of this meta-analysis.

The story is even more complicated because the latest Jick analysis reported above and the analysis by Farmer and associates used the exact same database and arrived at different conclusions![12] Of course, Jick et al believe their analysis is more refined and accurate. The editorial a month after the Jick article supports the conclusion that third-generation OCs have a higher risk of VT, citing a study that found acquired resistance to activated protein C to be more pronounced in users of these products.[13] There was no mention of the fact that these results could not be confirmed by other investigators.[14,15]

Perplexed by these disagreements, I called Organon (accused in an editorial by Professor David Skegg from the University of Otago in New Zealand that analyses of the General Practice Research Database sponsored by the pharmaceutical company have been withheld, implying that the results were unfavorable toward the third-generation products).[16] The major inconsistency in the studies that was pointed out to me was a quantitative and qualitative difference in the cases that were excluded from analysis. They further pointed out that all of their sponsored studies have not been withheld but have been published.

So what are we to think? I believe that the meta-analysis reviewed the same evidence I have reviewed and reached a different conclusion. I have no problem with that because meta-analyses of case-control and cohort studies are very subjective—actually only opinions because they reflect the interpretation of published literature by the authors. My opinion and your opinion are as valid as theirs. The difference in the analyses of the UK database is due to differences in the methods and the problem of trying to assess a clinical problem that has a low incidence; hence a small number of cases easily influenced by methods of analysis.

I remain convinced that the apparent differences associated with third-generation OCs were due to: 1) the marketing and preferential prescribing of new products; and 2) the characteristics of the patients for whom the new products were prescribed. There is a 3-to-4 fold increased risk of VTE associated with all low-dose OCs, a risk that is approximately one third that associated with pregnancy. Most studies have found smoking to be associated with arterial disease, not venous thrombosis. Because 99.85% of women who would test positively when screened for an inherited susceptibility for clotting will *not* have a clinical event, it is not cost-effective to perform routine screening prior to prescribing. However, screening for inherited disorders should be pursued in women with a previous episode of idiopathic VTE or a close positive family history (parent or sibling) of venous thrombosis. ❖

References

1. World Health Organization. *Lancet*. 1995;346: 1575-1582.
2. World Health Organization. *Lancet*. 1995;346: 1582-1588.
3. Jick H, et al. *Lancet*. 1995;346:1589-1593.
4. Bloemenkamp KW, et al. *Lancet*. 1995;346:1593-1596.
5. Spitzer WO, et al. *BMJ*. 1996;312:83-88.
6. Suissa S, et al. *Contraception*. 1997;56:141-146.
7. Lidegaard O, et al. *Contraception*. 1998;57:291-301.
8. Farmer RD, et al. *Lancet*. 1997;349:83-88.
9. Lewis MA, et al. *Hum Reprod*. 1999;14:1493-1499.
10. Bloemenkamp KW, et al. *Lancet*. 1995;346:1593-1596.
11. Bloemenkamp KW, et al. *Arch Intern Med*. 1999;159: 65-70.
12. Farmer RD, et al. *BMJ*. 2000;321:477-479.
13. Skegg DC. *BMJ*. 2000;321:190-191.
14. Schramm W, Heinemann LA. *Br J Haematol* 1997;98: 491-492.
15. Heinemann LA, et al. *Contraception*. 1998;58:321-322.
16. Skegg DC. *BMJ*. 2000;321:1171-1172.

Effects of Inhaled Glucocorticoids on Bone Density in Premenopausal Women

ABSTRACT & COMMENTARY

Synopsis: *Inhaled glucocorticoid therapy was associated with a dose-related decline in hip bone density in premenopausal women.*

Source: Israel E, et al. *N Engl J Med*. 2001;345: 941-947.

Inhaled glucocorticoids are the mainstay of treatment for asthma and other respiratory conditions. It is widely held that their use poses minimal long-term health risks. Israel and colleagues sought to

determine the effects, if any, upon bone density. To this end, they performed a prospective cohort study of premenopausal women. They recruited 3 groups: those not taking inhaled glucocorticoids; those taking 4-8 puffs daily; and those taking more than 8 puffs daily. Also, 109 women with 10 or more menses annually were enrolled between the ages of 18-45 years. Smokers were excluded as were those with any other medical conditions known to influence bone mass. Women who required oral glucocorticoids were excluded as were those taking any other substances known to influence bone density. All women were given calcium plus vitamin D (400 IU) supplements. Bone density was determined at baseline and at 0.5, 1, 2, and 3 years by dual-photon absorptiometry (Hologic®) in a single laboratory. A single investigator blind to subject status interpreted all results. Biochemical measures were also obtained at each visit.

There were no significant differences among the groups in respiratory status, physical activity, calcium intake, oral contraceptive use, or baseline bone density. There was a negative correlation between the average number of puffs per day of inhaled glucocorticoids and the annual change in bone density of total hip and at the trochanter. There was no association between glucocorticoid use or dose and bone density at femoral neck or lumbar spine across the 3-year observation interval. Urinary and serum measures of bone turnover (serum osteocalcin and parathyroid hormone and urinary N-telopeptide) were not consistently correlated with change in bone density. Israel et al note that a women who used inhaled glucocorticoids for 20 years premenopausally would experience sufficient bone loss to double her risk of hip fracture at age 65 based on bone density decline alone. However, they also note that women with osteopenia attributable to glucocorticoid use have a higher fracture rate than would be predicted from bone density alone. Glucocorticoid use apparently is a cause of bone fragility, which cannot be measured radiologically.

COMMENT BY SARAH L. BERGA, MD

Inhaled glucocorticoids are widely used for control of seasonal allergies, allergic rhinitis, and asthma. The prevailing assumption is that their use poses few medical risks, is devoid of nuisance side effects like sedation, is effective, and costs very little. There are studies, however, linking chronic inhaled or topical glucocorticoid use to an increased risk of osteoporosis and cataracts. For lipophilic compounds like steroids, systemic absorption from the lung is excellent. This is why there is reason to worry that the price one pays for short-term amelioration of respiratory conditions is long-term disability. The more serious the underlying respiratory condition, the more it may be worthwhile to assume these risks, particularly if there are no other equally effective medications. In weighing the pros and cons, it is important to remember that there are new medications that are especially effective for asthma control, namely, the leukotriene receptor antagonists, such as montelukast (Singulair®). These newer medications are much more selective in their targets (respiratory epithelium) and have fewer systemic side effects, but they are also much more expensive. Thus, health plans that offer pharmacy coverage tend to restrict their coverage of these selective compounds. The importance of this study is that it provides concrete data regarding the potential risks of inhaled glucocorticoids. In so doing, it creates the rationale for the use of safer, more targeted medications.

Another take-home message from this study is that the use of inhaled glucocorticoids should be added to the list of factors that increase the risk of osteoporosis. At midlife, women who have relied on inhaled glucocorticoids for the treatment of respiratory conditions should be offered an assessment of bone density, even if they had regular menses during their reproductive years. If they began the use of inhaled glucocorticoids in adolescence or childhood, the risk of osteoporosis and bone fragility is particularly heightened. It is not clear if there is any agent that can fully counteract the effect of glucocorticoids in women who must use them. After childbearing is complete, the use of bisphosphonates can be contemplated. Their use prior to the completion of childbearing is contraindicated because bisphosphonates are incorporated into the bone and then they slowly leach out. Therefore, even remote use may lead to incorporation of bisphosphonates into fetal bone during pregnancy. During reproductive years, the most that one can offer is oral contraceptives and adequate mineral and vitamin D intake. Exercise also stimulates bone accretion. While it is not clear that any combination of these prophylactic measures will fully counteract the effects of ongoing glucocorticoid exposure, one would recommend them anyway. In summary, it is particularly important to counsel women who use inhaled glucocorticoids about the potential risks of long-term osteoporosis and bone fracture. When feasible, an alternative treatment plan should be encouraged. It may fall to gynecologists to be the ones who sound the alarm and provide counseling about alternative medications and prophylactic measures. ❖

Special Feature

Use of Positron Emission Tomography in Cervical Cancer

By David M. Gershenson, MD

Because of progress related to pap smear screening programs over the past half-century, invasive cervical cancer has become a rather uncommon malignancy in the United States, with fewer than 13,000 new cases annually. However, cervical cancer remains one of the most common malignancies among women worldwide. Unlike the surgical staging systems of endometrial, ovarian, and vulvar cancers, the staging system for cervical cancer is clinical. Therefore, staging for cervical cancer uses only physical examination and commonly available diagnostic studies. In fact, information on the lymph node status—pelvic, para-aortic, and supraclavicular—assessed by surgery or imaging studies is not considered in this staging system. Nevertheless, we have known for quite some time that lymph node status is 1 of the most important prognostic factors in cervical cancer. Lymph node spread is a predominant mode of spread in this disease and generally follows an orderly pattern, with involvement of pelvic nodes initially and subsequent dissemination to para-aortic and then supraclavicular nodes. Importantly, failure to detect lymph node spread may result in failure to treat this site altogether or failure to completely eradicate tumor because of inadequate doses of irradiation.

Over the past 2 decades or so, several different imaging techniques have been used to assess lymph node involvement in cervical cancer patients. These have included lymphangiography, computed tomography (CT), and magnetic resonance imaging (MRI). Lymphangiography was used extensively at M.D. Anderson Cancer Center for several decades with excellent results. Some studies indicated that this technique was superior to CT in detecting lymph node spread from cervical cancer. However, this technique requires greater expertise in performing and interpreting; thus, it has fallen out of favor even at our institution. More recent studies have indicated that lymphangiography, CT, and MRI are equivalent in terms of detection of lymph node involvement.[1] However, the sensitivity of both techniques is unacceptably low. Hence, the emergence of pretreatment surgical staging for cervical cancer. At several centers, patients with newly diagnosed cervical cancer undergo extraperitoneal lymphadenectomy prior to definitive chemoradiation for advanced cervical cancer. In my view, the precise role of surgical staging for cervical cancer remains unclear. We currently do not perform this procedure on every new cervical patient but rather reserve it for patients with enlarged metastatic lymph nodes detected by imaging studies. However, the benefits of debulking grossly positive retroperitoneal lymph nodes in cervical cancer also remains controversial and unproven.

Over the past few years, the use of positron emission tomography (PET) scanning has been studied in patients with invasive cervical cancer with promising findings. This technique uses a derivative of glucose—fluorodeoxyglucose (FDG)—that is useful in imaging of solid tumors because of the high glycolytic rate of many malignancies. In 1999, Rose and colleagues reported on the use of PET scanning prior to surgical staging in 32 patients with stages IIB, IIIB, and IVA cervical cancer.[2] FDG was taken up by 91% of the cervical cancers. Six of 8 patients with positive para-aortic lymph nodes had PET scan evidence of para-aortic nodal metastasis. One of the 2 false-negatives had only 1 microscopic focus of metastasis. In the para-aortic nodes, PET scanning had a sensitivity of 75%, a specificity of 92%, a positive predictive value (PPV) of 75%, and a negative predictive value of 92%. FDG para-aortic nodal uptake conferred a relative risk of 9.0 for para-aortic nodal metastasis. All 11 of 17 patients with metastasis to pelvic lymph nodes were predicted by PET scanning ($P < .0001$); 5 of these patients had abnormalities on CT scans.

In a study from Germany, 35 patients with stages IB or II cervical cancer underwent FDG-PET scanning and MRI prior to radical hysterectomy and pelvic lymphadenectomy.[3] Histologic examination revealed lymph node metastasis in 11 of the 35 patients. This included 3 of 21 patients (14%) with stage IB disease and 8 of 14 (57%) with stage II disease. Nodal staging resulted in sensitivities of 0.91 with PET and 0.73 with MRI and specificities of 1.00 with PET and 0.83 with MRI. The PPV of PET was 1.00 and that for MRI was 0.67. The metastatic involvement of lymph node sites was identified at PET with a PPV of 0.90; at MRI, 0.64 ($P < .05$).

In a recently reported study from the Mallinckrodt Institute of Radiology in St. Louis, Grigsby and associates retrospectively compared the results of CT lymph node staging and whole-body FDG-PET in 101 consecutive patients with cervical cancer.[4] Patients were treated with standard irradiation and chemotherapy, as clinically indicated, and subsequently followed at 3-month intervals. No pretreatment surgical staging was performed in this group of patients. CT demonstrated abnormally enlarged pelvic lymph nodes in 20 (20%) and para-aortic lymph nodes in 7 (7%) of the 101 patients. PET demonstrated abnormal FDG uptake in pelvic lymph nodes in 67 (67%), in para-aortic lymph nodes in 21 (21%), and in supraclavicular

lymph nodes in 8 (8%). The 2-year progression-free survival, based solely on para-aortic lymph node status, was 64% in CT-negative and PET-negative patients, 18% in CT-negative and PET-positive patients, and 14% in CT-positive and PET-positive patients ($P < .0001$). A multivariate analysis demonstrated that the most significant prognostic factor for progression-free survival was the presence of positive para-aortic lymph nodes as detected by PET imaging ($P = .025$).

In summary, there is mounting evidence that PET scanning is currently the best technique for detection of lymph node spread from cervical cancer. Further, in the study by Grigsby et al, positive PET appears to be a major predictor of disease progression. While larger confirmatory studies will be necessary, I believe that PET will rapidly move into our armamentarium of diagnostic studies in patients with cervical cancer. Technology is already available to combine CT and PET so that the anatomic landmarks for sites of disease will be more precise. To what degree the introduction of CT/PET will influence the frequency of pretreatment surgical staging remains undetermined. ❖

References

1. Scheidler J, et al. *JAMA*. 1997;278:1096-1101.
2. Rose PG, et al. *J Clin Oncol*. 1999;17:41-45.
3. Reinhardt MJ, et al. *Radiology*. 2001;218:776-782.
4. Grigsby PW, et al. *J Clin Oncol*. 2001;19:3745-3749.

CME Questions

17. The following statements are true regarding the association between oral contraceptives and the risk of venous thromboembolism *except*:

a. All studies find an increased risk of venous thrombosis associated with third-generation oral contraceptives.
b. All oral contraceptives are associated with an increased risk of venous thrombosis.
c. A meta-analysis does not always reach the clinically correct conclusion.
d. Smoking is probably not a risk factor for venous thromboembolism.

18. Which of the following measures *cannot* be recommended to safeguard bone health during reproductive years?

a. Minimize the use of inhaled glucocorticoids
b. Exercise
c. Adequate mineral and vitamin D intake
d. Bisphosphonates
e. Oral contraceptives

Annual Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
OB/GYN Clinical Alert	0 7 4 3 - 8 3 5 4	9/27/01
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$219.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Willie Redmond — Telephone: 404/262-5448

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*: Donald R. Johnston, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*: Rob Kimball, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: OB/GYN Clinical Alert — 14. Issue Date for Circulation Data Below: November 2001

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			2019	2035
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1783	1735
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1783	1735
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			15	15
f. Total Free Distribution *(Sum of 15d and 15e)*			15	15
g. Total Distribution *(Sum of 15c and 15f)*			1798	1750
h. Copies Not Distributed			221	285
i. Total *(Sum of 15g, and h.*			2019	2035
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership — Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/01

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

In Future Issues:

Treatment of Vulvar Vestibulitis