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Postmenopausal Estrogen Therapy and Ovarian Cancer

ABSTRACT & COMMENTARY

Rodriguez and colleagues from the american cancer Society examined the association of postmenopausal estrogen use and ovarian cancer mortality in a prospective cohort study. The American Cancer Society Cancer Prevention Study II enrolled 676,306 postmenopausal women by a baseline questionnaire in 1982. Deaths in this cohort through 1996 accounted for 107,810 (15.9%) of the original group. After exclusions (premenopausal, unavailable information, hysterectomy, ovarian surgery), 211,581 postmenopausal women were left for analysis, with a total of 1497 ovarian cancer deaths. Estrogen use (ever use, past use, current use) was based on responses to the baseline questionnaire. The risk ratio for ovarian cancer mortality was adjusted for age, race, oral contraceptive use, number of live births, body mass index, age of menarche and menopause, and tubal ligation. The statistically significant increased adjusted risk ratios are presented in the Table.

Table

	No. of Deaths	Rate Ratio (similar to Relative Risk)
Ever use	255	1.23 (1.06-1.43)
≥ 10 years of use	31	2.20 (1.53-3.17)

These numbers indicated 64.4 ovarian cancer deaths per 100,000 users of estrogen for 10 or more years, compared with 26.4 for never users. Rodriguez et al further concluded that some risk persisted for up to 29 years after discontinuing estrogen. Rodriguez et al considered a possible mechanism for their conclusion, suggesting that ovarian cancer is more affected by lower gonadotropin levels than higher levels (this would not be consistent with the protective effect associated with oral contraceptives, or that estrogen directly stimulates ovarian cellular proliferation). (Rodriguez C, et al. *JAMA.* 2001;285:1460-1465).

COMMENT BY LEON SPEROFF, MD

There are so many things about this epidemiologic report that remind one of the similar circumstances surrounding the issue of

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INSIDE

postmenopausal hormone therapy and the risk of breast cancer.

Rodriguez et al argue that one of the reasons the results suggest causality is that the findings are similar to previously published case-control studies.[1-3] In fact, one of their references, that I did not cite, is a book chapter; in 2 of their cited studies the conclusions for long-term users were not statistically significant; and in the 1 statistically significant result, the finding applied only to serous carcinomas. I am not impressed with the quality of their reporting. Another example of selective reporting is the statement in the introduction of the current report that breast cancer incidence increases only after long-duration estrogen use, citing the Nurses' Health Study report in 1995, and neglecting to point out that the results of the American Cancer Society study with these same authors failed to support the Nurses' Health Study conclusion.[4]

One case-control study that examined long-term use did not find an increased risk.[5] The pooled analysis by Whittemore and colleagues of the 12 case-control studies up to 1992 could find no evidence for an association between ovarian cancer and estrogen therapy.[6] A meta-analysis in 1998 concluded that there was a 27% increase in risk of ovarian cancer with more than 10 years of estrogen use, but among the 6 studies included in this analysis, only 1 reported a statistically significant increase in risk with 10 or more years of therapy; and by definition, even the meta-analysis conclusion of a 27% increase in risk did not reach statistical significance (CI = 1.00-1.61).[7] In a more recent meta-analyis of 15 case-control studies, in the year 2000, Coughlin and associates could not find an association of estrogen therapy with ovarian cancer and no evidence of an effect with increasing duration of use.[8] To be complete, I will add to this list a re-analysis of 4 European case-control studies that found a statistically significant increased risk of ovarian cancer with estrogen use, but responsibly noted that it is essentially impossible to control in observational studies (case-control and cohort) for the possibility that hormone users and never users have different risks for ovarian cancer because they are not identical populations.[9]

It should also be noted that retrospective analyses have not detected any detrimental effect on prognosis after surgery for ovarian cancer in patients subsequently treated with hormones.[10,11]

The weakest link in the American Cancer Society Study is the fact that information regarding estrogen use was obtained from the single self-administered questionnaire in 1982. Despite the fact that it is touted as a large prospective study, the conclusion with some strength of association (the increase with users of 10 or more years) was based on 31 cases. But most of all, the results of the study do not represent further information added to a uniform, strong, and consistent story in the literature on this subject. Instead, the subject is similar to that of breast cancer risk and hormone therapy—many negative studies with some positive studies. The positive studies exhibit a strength of association that is not huge and could be due to the problems of small numbers and the attempt to compare 2 groups that may be basically dissimilar.

Epidemiologic evaluation of the effects of postmenopausal combined estrogen-progestin therapy will not be forthcoming for several years because of the relative recency of combined regimens. Pointing out that a combination of estrogen and progestin may prove to protect against ovarian cancer (similar to the results seen with oral contraceptives) is justified, but I would not make that the major part of my response to this current epidemiologic report. I would rather emphasize the small numbers, the

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weak associations, and the mixed story in the observational studies—all indicating either a very small or no effect. ❖

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Does Palliative Chemotherapy Palliate?

ABSTRACT & COMMENTARY

Synopsis: *Although objective responses are low, active palliation with chemotherapy is associated with substantive improvement in patients' emotional function and global QL, with overall costs that seem relatively modest.*

Source: Doyle C, et al. *J Clin Oncol.* 2001;19: 1266-1274.

Doyle and associates evaluated patient expectations, palliative outcomes of chemotherapy, and the inherent resource use in patients undergoing second- or third-line chemotherapy for recurrent or refractory advanced ovarian cancer. They used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) and Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaires to assess palliative benefit and an in-house questionnaire to gauge patient expectations. The minimal clinically important difference (MCID) was calculated by asking women to make a global rating of change and correlating this to the EORTC QLQ C30. Twenty-seven patients were accrued. Objective response was documented on 7 of 27. The median survival was 11 months. Sixty-five percent of women expected that chemotherapy would make them live longer and 42% believed that it would cure them. After 2 cycles, quality of life (QL) improvement was seen particularly in global function (11 of 21), and emotional function was sustained for a median of 2 and 3 months, respectively, in these categories. The MCID was calculated to be 0.39 on a 7-point scale for physical function and 0.13 for global function. The mean total cost per patient for the study period was Can $12,500. Doyle et al concluded that patient expectations from these treatments are often unrealistic. Although objective responses are low, active palliation with chemotherapy is associated with substantive improvement in patients' emotional function and global QL, with overall costs that seem modest.

COMMENT BY DAVID M. GERSHENSON, MD

When patients with epithelial ovarian cancer develop a recurrence, we know that the primary objective is palliation since only a tiny fraction is cured. The average survival after diagnosis of recurrence is in the range of 1 year. At each point in their course of relapse, patients and their physicians must weigh the benefits of treatment against the risks and toxicities. There is an increasing body of literature on the quality of life of patients with ovarian cancer, both during primary treatment and during treatment of relapsed disease. Although this study contains a small number of patients, the observations are consistent with my perceptions of treating this disease for the past 2 decades. It is of utmost importance for physicians to be completely honest in counseling patients and their families about treatment, side effects, probability of response, and prognosis. However, one must balance truth with hope. How much information does the patient want? Certainly, not all patients request or desire details and statistics about prognosis. Interestingly, the majority had hope of prolonged survival, but a high proportion of patients had unrealistic expectations about cure. A significant proportion of patients derived palliation from chemotherapy. As Doyle et al point out, however, we usually think of "palliation" as relief of physical symptoms; they include improvement in emotional well being as palliation, and I definitely agree with their assessment. Studies such as this will continue to improve the knowledge base of caregivers of ovarian cancer patients and will translate into an enhanced doctor-patient relationship for those who listen. ❖

Microinvasive Carcinoma in Women with Cytologic Diagnosis of LGSIL

ABSTRACT & COMMENTARY

Synopsis: *Women who have LGSIL cytology reports should undergo colposcopic evaluation.*

Source: Law KS, et al. *J Reprod Med*. 2001;46:61-64.

The purpose of this article was to determine the actual disease that was present when a Pap smear was reported as low-grade squamous intraepithelial lesion (LGSIL). In order to make this determination, all cytology specimens from July 1994 through February 1998 (128,925 samples) were reviewed for a diagnosis of LGSIL. Eight hundred seventy-seven (0.7%) of the smears were reported as LGSIL. All women with this diagnosis were referred to the colposcopy clinic and approximately 90% had that procedure performed. Women who did not appear for colposcopy were excluded from the study. A total of 790 women with an LGSIL report and colposcopy comprised the study material for this paper.

A total of 145 women were found to have CIN 2 or CIN 3. Sixty-three percent of these were found at the time of initial colposcopy and biopsy; the remaining cases were found through conization or hysterectomy. A few women (13) had the high-grade lesion detected during follow-up after a negative colposcopy. Interestingly, there were 16 cases of microinvasive squamous cancer detected. Law and associates state that this high rate of cancer reflects the high prevalence in their country (Taiwan.)

COMMENT BY KENNETH L. NOLLER, MD

In recent years, there has been great interest in following women with cervical intraepithelial neoplasia, grade 1 (CIN 1) without treatment. Fifty to 70% of women who are followed will have spontaneous resolution of their disease, with the remaining women being approximately equally divided between persistence of CIN 1 and progression to CIN 2/3. This approach—follow-up without treatment—seems particularly advantageous for young, nulliparous women.

Unfortunately, the fact that many women with CIN 1 (low-grade changes) are now followed without treatment has mysteriously morphed into the recommendation that women with LGSIL Pap smears be followed with cytology only. That is a particularly unfortunate concept, since, as this article clearly shows, a significant fraction of women with LGSIL cytology reports have high-grade lesions present. At the present time, it seems reasonable (and might even be cost effective) for all women with LGSIL changes to have colposcopy. If no lesion or only a low-grade lesion is identified, the patient can then be followed without therapy. On the other hand, if a high-grade lesion is discovered, appropriate therapy can be instituted. While the rate of high-grade lesions in the United States among women with LGSIL cytology is considerably less than was found in this Taiwan-based study, nonetheless, high-grade lesions occur with significance frequency that colposcopy is warranted. ❖

Standard-Dose Intravenous Cisplatin vs. Moderately High-Dose Carboplatin

ABSTRACT & COMMENTARY

Synopsis: *An experimental regimen including moderately high-dose IV carboplatin followed by IP paclitaxel and IV cisplatin yielded a significant improvement in progression-free survival when compared with a standard regimen of IV cisplatin and paclitaxel.*

Source: Markman M, et al. *J Clin Oncol*. 2001;19: 1001-1007.

In a report of an intergroup study involving 3 cooperative groups, Markman and colleagues compared the progression-free and overall survival in small-volume residual ovarian cancer after treatment with intravenous (IV) cisplatin and paclitaxel for 6 cycles, or an experimental regimen of IV moderately high-dose carboplatin for 2 cycles followed by IV paclitaxel and intraperitoneal cisplatin for 6 cycles. Of the 523 patients who entered this trial, 462 were determined to be assessable, with prognostic factors well balanced between the treatments. Neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities were greater in the experimental arm. As a result, 18% of the patients received less than 2 courses of IP therapy. Progression-free survival was superior for patients randomized to the experimental treatment arm (median, 28 vs 22 months; relative risk, 0.78; log-rank $P = .01$). There was a borderline improvement in overall survival associated with this regimen (median, 63 vs 52 months; relative risk, 0.81; $P = .05$). Markman et al concluded that the experimental regimen including moderately high-dose IV carboplatin followed by IV paclitaxel and intraperitoneal (IP) cisplatin yielded

a significant improvement in progression-free survival when compared with a standard regimen of IV cisplatin and paclitaxel. Because the improvement in overall survival was of borderline statistical significance and toxicity was greater, Markman et al did not recommend the experimental arm for routine use.

COMMENT BY DAVID M. GERSHENSON, MD

After more than 2 decades of study, we still do not know the role of IP chemotherapy in the management of epithelial ovarian cancer. Several phase II clinical trials of IP chemotherapy in patients with recurrent ovarian cancer have demonstrated antitumor activity of a variety of drugs. However, only through direct comparisons with IV chemotherapy can we understand the true benefit of such an approach. We certainly do know that IP chemotherapy is feasible and generally safe. A previous intergroup study comparing IV cyclophosphamide/IP cisplatin with IV cyclophosphamide/IV cisplatin showed a superior overall survival for the IP group (median, 49 vs 41 months).[1] However, this study was criticized for several design and analysis flaws. The present study certainly does not answer the question as to whether IP chemotherapy is advantageous as primary therapy for advanced epithelial ovarian cancer. The survival advantage was borderline, and the "IP arm" really was a package that included moderately high-dose IV carboplatin (a design flaw that the investigators recognized at the outset). The current Gynecologic Oncology Group (GOG) randomized trial studying the role of IP cisplatin and paclitaxel with IV paclitaxel should provide a better answer. If that study is negative, that may sound an end to the use of IP chemotherapy for ovarian cancer. ❖

Reference

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Estrogen Receptor α Is a Critical Link in Protection Against Brain Injury

ABSTRACT & COMMENTARY

Synopsis: *Using a mouse model of ischemic stroke, the researchers demonstrate that ERα, but not ERβ, mediates the neuroprotective effects of estradiol exposure.*

Source: Dubal D, et al. *Proc Natl Acad Sci Am*. 2001; 98:1952-1957.

Dubal and associates have been exploring the mechanisms by which estrogen confers neuroprotection. They previously demonstrated that the neuroprotective effects of 17β-estradiol are not rapid and require a period of pretreatment, suggesting that ER-mediated alteration of gene expression is required to afford neuroprotection. Furthermore, in response to ischemic injury, ERα mRNA is up-regulated in the brain in the presence and the absence of estradiol. In contrast, injury down-regulates ERβ mRNA, and this down-regulation is prevented by advance estradiol exposure. Finally, this investigative team has shown that the estrogen isomer 17α-estradiol, which has 100-fold less affinity for ERs, fails to protect against brain injury and that the protective effects of 17β-estradiol are prevented by ICI 182,780, an ER antagonist. To further define the role of ERα and ERβ in mediating the neuroprotection effects of 17β-estradiol, they examined the effects of estradiol in genetically modified mice lacking either ERα or ERβ. Knock-out (KO) mice were compared to their respective wild-type strains. Ovariectomy was followed by estradiol replacement to a standard physiological level or placebo. One week later, ischemia was produced and then the mice brains were examined histologically after 24 h. During the ischemia, doppler monitored cerebral blood flow. In both wild-type strains, estradiol decreased total ischemic injury by more than 50% compared with oil-treated controls. In ERαKO mice, estradiol failed to exert any protection against infarct. In marked contrast, in ERβKO mice, estradiol exerted profound protective effects against brain injury. The results were not explained by differences in cerebral blood flow during or after the ischemia.

COMMENT BY SARAH L. BERGA, MD

This study bears directly on the decision as to which estrogen is best for long-term use by postmenopausal women. If the results of this study hold for humans, then what is needed is an agent that acts via ERα. One such agent is 17β-estradiol. Compounds that are antagonists for ERα are unlikely to protect against ischemic CNS injury. One such agent is raloxifene. Phytoestrogens bind predominantly to ERβ. Thus, while it might be advantageous to incorporate them into one's diet (see Clarkson study reviewed in the April 2001 issue of *OB/GYN Clinical Alert*), but they are unlikely to be a worthy replacement for estradiol. A prime benefit of agents that are ERα antagonists is that they don't stimulate endometrial growth. As reviewed earlier this year, however, the vaginal tissues, including the smooth muscle cells, predominantly express ERα.[1] Thus, while it is nice to think we might find an agent that doesn't stimulate endometrium, it seems unlikely that any such agent will confer full neuroprotection or even ameliorate geni-

tourinary atrophy. At the risk of sounding brazen, I would like to suggest that it is easier to do a hysterectomy for endometrial hyperplasia or persistent breakthrough bleeding than it is to restore an infarcted brain. Perhaps we will never find the perfect agent. In the meantime, it seems prudent to recommend the estrogen that mother nature designed for women, namely, 17β-estradiol, given in physiological doses. ❖

Reference

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Special Feature

Better Use of Technology Diminishes Need for Invasive Testing

By John C. Hobbins, MD

In 1955, the following statement appeared in the *Lancet*: "Although transabdominal puncture of the uterus has been carried out often for therapeutic and experimental reasons without accident, mere curiosity does not justify the procedure and its practical value in probably limited in the human. If the results are confirmed in animals, however, it might become of great significance in veterinary practice."

Despite this prophecy, in the 1970s, amniocentesis was offered to many patients of the AMA, simply because it became possible to do karyotypic analysis on cultured amniocytes. Amniocentesis at that time involved introducing a needle into the uterus midway between the patient's uterine fundus and the symphysis pubis. Sometimes ultrasound was used to mark a preferable needle insertion site, after which the patient walked to another area where a clinician would insert a needle through the "marked" area. Later real-time ultrasound enabled the operator to guide a needle into a desired place under simultaneous ultrasound guidance. Although data were sparse, the observation that the risk of the pre real-time amniocentesis seemed to be only marginally greater than the post real-time method was a testimonial to the resilience of pregnancy in general. Nevertheless, this technique does carry some risk, and between 50 to 100 per 1000 fetuses will be lost due to the second trimester procedure.

Now that the triple or "quad" screen has come into being, the tests can better adjust the fetal DS risk for a given patient, most often below the risk of amniocentesis.

An article in *JAMA* (soon to be reviewed) has recently ignited controversy regarding the efficacy of the genetic sonogram to more precisely adjust Down syndrome risk so that amniocentesis can be avoided when a risk/benefit mismatch exists. Interestingly, although the authors of this article criticize the benefit of the genetic sonogram, their own data support the reassuring value of a "negative sonogram."

In any case, we have recently found that about 60% of AMA patients seeking prenatal testing with a triple screen and/or a sonogram decline amniocentesis. Hopefully, when the method of fetal cell separation from maternal blood comes to fruition, there will be much less need for amniocentesis. The point is that as some newer techniques become available and older concepts change, fewer invasive techniques will be required.

Percutaneous umbilical blood sampling (PUBS) is a diagnostic technique that emerged in the late 1980s. The original technique for obtaining fetal blood involved the use of an endoscope with which one could draw blood from the umbilical cord under direct visualization. PUBS is less invasive than fetoscopy, but can be tricky to perform and, as is usually the case, the fetal risk is greater than originally reported. The more common indications include rapid karyotyping, diagnosis of fetal anemia from Rh and Kell sensitization, and fetal infections such as Parvovirus. It has also been used to determine fetal blood gas status, for example, in IUGR.

However, for good reason, we are now going through a PUBS "recession." In fact, it is now difficult to find a legitimate reason to do PUBS, and even in busy high-risk centers, there are not enough cases to adequately train perinatal fellows in the performance of this procedure.

Why the paucity of PUBS procedures? Today, through the ability to exclude fetal anemia noninvasively through assessment of doppler waveform analysis of the fetal middle cerebral arteries, amniocentesis is now rarely used in our institution to predict fetal red blood cell breakdown through AOD analysis, and PUBS is only used in cases where there is strong evidence that it would have therapeutic benefit. Rapid karyotyping, previously a PUBS diagnostic staple, can now be accomplished through fluorescent in situ hybridization (FISH) on amniotic fluid cells, enabling clinicians to substitute a less risky procedure for a more invasive one. Since fetal dopplers are so effective at ruling out metabolic acidemia, PUBS is rarely needed in IUGR.

Even with invasive lifesaving fetal therapeutic maneuvers, less invasive measures can help to better

select patients whose fetuses would truly benefit from their procedures. For example, in fetal bladder obstruction, it is possible to determine with ultrasound (through the echogenicity of the renal cortex and through electrolyte analysis of aspirated fetal urine) which fetuses are potentially salvageable. Also, although the ultimate surgical technique for fetal diaphragmatic hernia is still up in the air, a rough ultrasound estimate of fetal lung volume can better select fetuses that might possibly benefit from some type of in utero surgery.

In some clinical dilemmas, a more invasive technique may become preferable to a less invasive one, as long it is proven to be more effective. For example, at the moment it is unclear whether endoscopic laser ablation of communicating placental vessels in twin-to-twin transfusion syndrome is of greater therapeutic benefit than repetitive amniocentesis. The latter less invasive measure has been associated with fatal salvage in about 60% of cases, but those investigators using the endoscopic technique are beginning to report a better long- term outcome with laser compared with contemporary data from studies using therapeutic amniocentesis. However, since the populations in the existing studies may not be comparable, the only way to evaluate the best approach would be through randomized clinical trials. After some initial bickering between the two factions, RCTS are being initiated in Europe and the in the United States. Hopefully, these trials will yield usable results.

Where can we go from here? Investigators have been working for more than a decade to separate fetal cells from the maternal circulation, and still the kinks have not been ironed out. When they are, only a few amniocenteses will be performed for only those who really need them. PUBS will undoubtedly be used only where direct access to the fetal circulation is absolutely necessary, such as in intrauterine transfusion, or to deliver a medication directly to the fetus, eg, with a cardiac arrhythmia that is refractory to standard treatment.

"Open" surgical procedures to repair diaphragmatic hernia or to circumvent urethral obstructions are already being replaced by endoscopic techniques, and although the efficacy of in utero repair of spina bifida has definitely not yet been proven, it is likely that the endoscope will ultimately be the vehicle of choice, if legitimate research shows a benefit.

In many clinical situations in obstetrics, the benefit of experience has allowed clinicians to replace the phrase "don't just stand there, do something" with the concept of "don't just do something, stand there." In prenatal diagnosis and in many fetal therapeutic ventures "standing there" may not be the best option, but using the least risky (and often glitzy) method to obtain a result is what the art of medicine is all about. ❖

CME Questions

14. Among women with LGSIL cytology, the most appropriate next step in their management would be:

a. immediate repeat cytology.
b. repeat cytology at 3 month intervals for 1 year.
c. colposcopy and directed biopsy.
d. loop excision or cold knife conization of the cervix.

15. The following statements are true of the association between ovarian cancer and postmenopausal hormone therapy *except*:

a. The epidemiologic data thus far include only women using unopposed estrogen regimens.
b. There is no evidence that short-term estrogen therapy increases the risk of ovarian cancer.
c. Survivors of ovarian cancer should not use postmenopausal estrogen therapy.
d. Hopefully, combined postmenopausal regimens of estrogen and progestin will protect against ovarian cancer like combined oral contraceptives.

16. A recent phase III randomized intergroup study comparing moderately high-dose carboplatin plus IV paclitaxel/IP cisplatin with the standard regimen of IV paclitaxel/IV cisplatin showed the following:

a. Improved progression-free survival and borderline improvement in overall survival for the experimental arm
b. Improved progression-free survival and significantly improved overall survival for the experimental arm
c. Improved progression-free survival but worse overall survival for the experimental arm
d. Worse progression-free survival and worse overall survival for the experimental arm
e. Same progression-free survival but improved overall survival for the experimental arm

17. In a recent study from Canada on the expectations of patients with recurrent ovarian cancer regarding the effects of palliative chemotherapy, which of the following best characterizes the findings?

a. The majority expected prolonged survival but expectations for cure were unrealistic.
b. The majority expected prolonged survival and expectations for cure were realistic.
c. The majority did not expect prolonged survival and expectations for cure were unrealistic.
d. The majority did not expect either prolonged survival or cure.

18. Which of the following agents is likely to protect against ischemic CNS injury?

a. 17α-estradiol
b. raloxifene
c. phytoestrogens
d. 17β-estradiol
e. all of the above

Attention Subscribers. . .

A special supplement to OB/GYN Clinical Alert titled "Antibiotics Anonymous Redux" is included with this edition, as a bonus to our subscribers. The supplement takes a tongue-in-cheek look at a problem facing many physicians: over-prescription of antibiotics. Here is an editorial note from Stan Deresinski, MD, editor of Infectious Disease Alert:

The problem of antibiotic resistance continues to worsen. An important contribution to this problem is the inappropriate prescription of antibiotics by physicians. For example, excess prescription of antibiotics for respiratory tract infections, particularly in children, has been identified as an important factor in the emergence of penicillin-resistant Streptococcus pneumoniae. Indeed, it has been suggested that some physicians have lost control over their antibiotic prescribing—that they have become, in effect, antibiotic dependent. I have, as a consequence, devised a questionnaire for the diagnosis of this dreaded addiction afflicting practicing physicians. If the answer to one or more of these questions is yes, you have a problem!. . .❖

In Future Issues:

Management Strategies for Patients With Atypical Squamous Cells of Undetermined Significance

A supplement to OB/GYN Clinical Alert, May 2001 — published by *The Coding Institute*

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OB-GYN CODING ALERT

The practical monthly advisor for ethically optimizing coding reimbursement and efficiency in ob-gyn offices and clinics

Coding Q & A:
Get Expert Advice to Your Most Challenging Ob-Gyn Questions

Laparoscopy

Question: *When billing a diagnostic laparoscopy with lysis of adhesions (58660) along with a laparoscopy with aspiration of a cyst (49322), should the second procedure have a modifier -51 or a modifier -59?*

Alabama Subscriber

Answer: The most extensive procedure is always listed first on the claim form. In this case, the laparoscopic lysis of adhesions (58660, *laparoscopy, surgical; with lysis of adhesions [salpingolysis, ovariolysis] [separate procedure]*) is the higher-valued code so it will be listed first with modifier -59 (*distinct procedural service*) to let the payer know that it was distinct from the aspiration as it is listed in CPT as a "separate procedure." Code 49322 (*laparoscopy, surgical; with aspiration of cavity or cyst [e.g., ovarian cyst] [single or multiple]*) will be listed second with modifier -51 (*multiple procedures*).

If the values of these two procedures had been reversed so that the second code listed was the "separate procedure" code that required the -59 to get paid, you would list both modifiers on the second code, but list -59 first. Modifier -59 tells the insurance payer that you should be reimbursed for the service, and -51 indicates how much.

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Blood Test and/or Injection

Question: *How do I code a claim when a patient comes in for a blood test and/or injection? How can we appeal if it is denied due to being a part of the office visit?*

Nebraska Subscriber

Answer: Many payers believe evaluation and management (E/M) codes include what they term "incidental" procedures that do not require much physician time or work. This may include things like an injection or collection of a blood sample for testing. However, CPT states specifically that these services can be reported separately because the purpose of the E/M code is to report only E/M services, not other procedures or services identified by another code (see page 2 of CPT 2001, professional edition).

Unless the payer has specifically excluded an injection or blood draw from being reimbursed at the same time as an E/M service as part of its policy manual, you may code either one in addition. You may, however, have to add modifier -25 (*significant, separately identifiable evaluation and management service by the same physician on the same day of the procedure or other service*) to the E/M service to indicate that it was separate from the other services provided that day.

If the only reason for the visit was the blood draw or injection and no E/M service was provided or documented, code for the blood draw or injection.

&

Vaginal Delivery

Question: *Is there a code for operative vaginal delivery with forceps and vacuum? My hospital has been billing for a global standard vaginal delivery fee, regardless of the delivery mode. However, they bill a higher rate for vaginal birth after cesarean (VBAC) — 59610-59614. Is there a way to notify the insurance carriers of an increased risk and increased liability for these procedures and therefore obtain better reimbursement compared to vaginal delivery?*

Charles Deborah, MD
Mason City, Iowa

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Answer: The definition of maternity services in CPT 2001 (page 201 of the professional edition) states that vaginal delivery includes episiotomy and forceps (if used). The American College of Obstetricians and Gynecologists in its coding manual *Components of Correct Procedural Coding* has indicated that vacuum extraction is also included as part of the service and should not be coded separately. VBAC has its own specific CPT code because the service requires more intense physician work routinely.

If a physician believes that the use of forceps or vacuum extraction for a particular patient was much more work than is usually the case and this additional work has been documented, you have the option of billing the insurance company for the global service using modifier -22 for unusual procedural services. You would of course need to send in the documentation with the claim.

New Versus Established Patient

Question: *A nurse midwife is joining our practice, a professional corporation. Some of her patients will likely follow her here. Would these patients be new patients or established patients at our office?*

Ohio Subscriber

Answer: If the nurse midwife bills for the patient care, the patient would be established to the practice because a physician (or other qualified care-giver) of the same specialty has seen her within the last three years. CPT language does not directly address the nurse midwife in its current definition, but the implication is that the qualified care-giver would also meet this definition. It is less clear whether this same interpretation would apply if the nurse midwife was not directly billing for the services, but rather if the services were billed under the physician provider number following "incident to" rules. Check with your payer before billing if you are unsure.

Laminaria Removal

Question: *Can I bill 57415 when removing laminaria in the operating room that had been inserted the day before a second-trimester pregnancy termination?*

Michigan Subscriber

Answer: Code 57415 (*removal of impacted vaginal foreign body [separate procedure] under anesthesia*) would not be appropriate in this circumstance. It would be highly unlikely that a payer would accept the premise that a laminaria placed the day before the pregnancy termination was an "impacted vaginal foreign body." Simply bill the surgery (probably 59855 for induced abortion) and consider removal of the laminaria part of the exam and prep work involved in the procedure.

— Source for answers to "Coding Q & A" is ***Melanie Witt, RN, CPC, MA,*** *an independent coding educator based in Fredericksburg, Va.* ❑

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Antibiotics Anonymous Redux*

By Stan Deresinski, MD, FACP, Editor, Infectious Disease Alert

Are *You* Antibiotic Dependent?

- ❑ Do you prescribe antibiotics to relieve tension?
- ❑ Do you prescribe antibiotics more than other physicians but are able to hide it?
- ❑ Do you sometimes feel guilty about the way you prescribe antibiotics?
- ❑ Do you have a strong urge to prescribe antibiotics at a particular time of day?
- ❑ Have you lost ambition since you began prescribing antibiotics in this way?
- ❑ Has another physician advised you to stop or cut down your prescribing?
- ❑ Are you harder to get along with when you are heavily prescribing?
- ❑ Have you ever tried to cut back?
- ❑ Do you have difficulty sleeping a full night?
- ❑ Have you ever been in trouble with the antibiotic police?
- ❑ Have you ever done anything while prescribing that you don't remember (have a blackout)?
- ❑ Have you ever promised yourself you would cut back on your prescribing and then broken that promise?
- ❑ Have you ever tried to convince people that you were not prescribing antibiotics when you were?
- ❑ Do you wish people would mind their own business about your antibiotic prescribing—that they stop telling you what to do?
- ❑ Have you ever switched from one kind of antibiotic to another in the hope that this would keep you from going over the edge?
- ❑ Have you had to have an eye-opener (ie, prescribed an antibiotic immediately upon awakening, in the last year)?
- ❑ Do you envy people who can prescribe antibiotics without getting into trouble?

For those who have answered yes to one or more of these questions, I have begun the development of a 12-step program. Unfortunately, I have only been able to develop half of a 12-step program.

- ❑ You must admit that you are powerless over your antibiotic prescribing.
- ❑ You must believe that a power (an antibiotic guru) greater than yourself can restore you to sanity.
- ❑ You must make a decision to turn your will and life over to the care of that power.
- ❑ You must make a searching and fearless moral inventory of yourself.
- ❑ You must admit to the power and to yourself the exact nature of your misprescribing.
- ❑ You must humbly ask the power to remove your antibiotic shortcomings.

* *Lockwood WR. Letter: Antibiotics anonymous. N Engl J Med 1974;290:465-466.*