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Tamoxifen and Breast Cancer Incidence Among Women with Inherited Mutations in BRCA1 and BRCA2

ABSTRACT & COMMENTARY

The rationale for the present analysis is compelling. King and colleagues hypothesized that tamoxifen would protect against the development of breast cancer only in women prone to breast cancers that express estrogen receptors (ER). They note that current data show that 76% of breast tumors found in women who carry the BRCA2 mutation are ER-positive. In contrast, 83% of breast cancers found in women who carry a BRCA1 mutation are ER-negative. They thus reasoned that tamoxifen use would reduce the likelihood of developing a breast carcinoma in women who carry the BRCA2 mutation but not the BRCA1 mutation.

To test this hypothesis, King et al determined the BRCA mutation status of the 288 women who developed breast cancer while participating in the Breast Cancer Prevention Trial (BCPT). The BCPT was a randomized, double-blind trial conducted from 1992-1998. Tamoxifen was given to 13,388 women older than age 35 who were determined to be at high risk of developing invasive breast cancer. High risk was defined by any one of the following: the Gail model;[1] age > 60 years; or lobular carcinoma in situ. Eighty percent of participants were followed for 3 years and 65% for 5 years.

The sample resulted in 320 cases of breast cancer (2.4% of the study group), but BRCA mutation status could only be determined in 288. Of those, only 19 (6.6%) had a BRCA mutation; 11 had BRCA2 and 8 had BRCA1. The BRCA mutation status of the women who did not develop breast cancer is unknown. Of those with BRCA1 mutations who developed breast cancer, 5 received tamoxifen and 3 got placebo. King et al calculated that tamoxifen use was associated in BRCA1 with a relative risk of 1.67 with a confidence interval of 0.32-10.70. Of those with BRCA2 mutations who developed breast cancer, 3 got tamoxifen and 8 received placebo. They calculated a relative risk of 0.38 for

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tamoxifen use, with a confidence interval of 0.06-1.56 (statistically nonsignificant). (King MC, et al. *JAMA*. 2001;286:2251-2256.)

COMMENT BY SARAH L. BERGA, MD

King et al posed an interesting question that had its genesis in their appreciation of the molecular biology of breast cancer. Unfortunately, the data set they chose to mine was relatively small. While the results do not contradict their hypothesis, they certainly do not prove it either. The most obvious limitation was the paucity of cases that were BRCA-positive. If one ignores the confidence intervals, the relative risks are impressive. But the confidence intervals are wide and include 1.0, so the results are not statistically significant.

There are other limitations to consider in interpreting the study. First, the hypothesis is based on some assumptions that may not be true. King et al state that tamoxifen acts as an anti-estrogen in breast tissue. Would that the world were so clear. There are annoying complexities that get overlooked by that statement, including the fact that there is more than one estrogen receptor subtype in breast tissue and that tamoxifen may be an antagonist for ER-alpha, but an agonist for ER-beta. Also, the main metabolite of tamoxifen is 4-hydroxytamoxifen and it may behave as an estrogen in some tissues. In an in vitro culture system, tamoxifen may act as an inhibitor of cell growth of breast cancer cell lines. However, in an in vitro model, tamoxifen is not metabolized and the interaction between the glandular and stromal elements of breast tissue is removed. Thus, cell culture results may not tell us what happens in vivo. Further, when tamoxifen is given to premenopausal women, it increases FSH concentrations. This in turn drives folliculogenesis and raises estrogen levels. Thus, tamoxifen use may result in a different hormonal milieu in pre- vs. postmenopausal women. The sample size is too small to address this issue. Finally, King et al note that in the whole cohort, tamoxifen use appeared to protect against the development of breast cancer. However, none of the participants has yet been followed for more than 10 years, so it is unclear how long the protective effect lasts (assuming that it is real).

My main reason for reviewing this article is to alert you to the fact that the small sample size precludes firm conclusions. I realize that the hypothesis is compelling. The concept being tested may be true. But the present data do not help us to know if it is. Thus it seems premature to act on these data clinically. It would be nice to know if tamoxifen is likely to protect against the development of breast cancer and, if so, in what populations it is protective. It would also be nice to know the mechanisms underlying its putative protective actions. A recent study by O'Meara and colleagues (which I reviewed in a recent issue of *OB/GYN Clinical Alert*) found that estrogen use by breast cancer survivors improves survival and reduces recurrences.[2,3] For all we presently know, tamoxifen may exert its protective actions by acting as an estrogen rather than an anti-estrogen in vivo at the level of the breast. At present, we really have no clinical guidelines as to who should use tamoxifen as prophylaxis against breast cancer and for how long. The risks and benefits of long-term tamoxifen use are a matter of conjecture, but its extended use is not necessarily benign. ❖

References

1. Gail MH, et al. *J Natl Cancer Inst*. 1999;91: 1829-1846.
2. O'Meara ES, et al. *J Natl Cancer Inst*. 2001;93: 754-761.
3. Berga, SL. *OB/GYN Clinical Alert*. 2001;18(3):17-18.

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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, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Noller and Dr. Hobbins report no relationships related to this field of study.

Important New Monkey Study from Tom Clarkson

ABSTRACT & COMMENTARY

Synopsis: *Tibolone treatment does not increase coronary artery atherosclerosis, and an equal reduction in atherosclerosis is seen with unopposed conjugated equine estrogen treatment and with conjugated equine estrogen combined with medroxyprogesterone acetate.*

Source: Clarkson TB, et al. *J Clin Endocrinol Metab.* 2001;86:5396-5404.

Tom clarkson and associates at the wake forest University School of Medicine report an important new study using their monkey model for the study of atherosclerosis. In this 2-year-long randomized trial, a total of 151 monkeys with surgical menopause were fed an atherogenic diet and divided into groups comparing the placebo response to high and low doses of tibolone, unopposed conjugated equine estrogens, and combined conjugated estrogens and medroxyprogesterone acetate. The daily doses of tibolone were equivalent to women's doses of 3.0 mg and 0.75 mg (human studies with tibolone have used 1.25 mg and 2.5 mg daily). The Premarin dose was equivalent to a little lower than 0.625 mg (Premarin) daily in women, and the combined estrogen and medroxyprogesterone acetate dose was equivalent to the daily regimen of PremPro (0.625/2.5). The observed changes in circulating lipids were similar to those reported in humans. Estrogen and combined estrogen-medroxyprogesterone acetate raised triglycerides and HDL-cholesterol, and lowered LDL-cholesterol. Tibolone lowered HDL-cholesterol, and in the high dose, increased LDL-cholesterol (this has not been observed with the doses used in women). Despite the "adverse" effect on lipids, the extent of coronary artery atherosclerosis was no different comparing the tibolone group with the placebo group. In fact, the tibolone animals even had slightly less atherosclerosis than the control animals. As expected, unopposed estrogen treatment reduced plaque size and intimal area in the coronary arteries with atherosclerosis, and there was no significant difference comparing the unopposed estrogen group with the estrogen-medroxyprogesterone acetate combination. Tibolone treatment increased bone mineral density a little more than estrogen treatment. Thus Clarkson et al concluded that tibolone treatment did not have an adverse effect on coronary artery atherosclerosis.

COMMENT BY LEON SPEROFF, MD

This is an important research report for 2 reasons. First, there has been concern that tibolone would have a negative effect on atherosclerosis because it lowers HDL-cholesterol. Second, concern has been raised that the daily presence of medroxyprogesterone acetate attenuates estrogen's beneficial actions on the vascular system.

Tibolone is metabolized into 3 steroid isomers with varying estrogenic, progestogenic, and androgenic properties. The metabolites differ in their activities and dominance according to the target tissue. Thus, tibolone provides estrogenic effects on bone and hot flushing, but it induces atrophy of the endometrium.[1] In the endometrium, tibolone is converted locally (by endometrial 3 beta-hydroxysteroid dehydrogenase/isomerase) to its Δ4-progestational isomer, explaining its nonproliferative effect on the endometrium.[2] The 3α-hydroxy and 3β-hydroxy metabolites bind only to the estrogen receptor, but the Δ4-isomer binds to the progesterone and androgen receptors. The decrease in HDL-cholesterol also indicates Δ4-isomer activity. Blood levels of the 3 metabolites in the monkeys were comparable to those measured in women receiving the standard doses of 1.25-2.50 mg/d.

Its beneficial impact on bone (2.5 mg dose) is comparable to or even better than standard hormonal therapy.[3] In a randomized trial, tibolone increased bone density over 3 years in contrast to 0.625 mg conjugated estrogens and 10 mg medroxyprogesterone acetate in a sequential regimen, in which bone density was maintained after an increase limited to the first 6 months.[4] Tibolone has an estrogenic effect on the vagina, and women report improvements in the symptoms of vaginal dryness and dyspareunia, and an increase in sexual enjoyment and libido.[5,6] A major advantage of tibolone (2.5 mg daily) is its low (10-20%) incidence of bleeding.[1] In a randomized trial comparing tibolone and continuous combined estrogen-progestin therapy, there was less breast tenderness and 50% less bleeding and spotting with tibolone.[7] Because tibolone inhibits breast cell proliferation in vitro and decreases breast density on mammography, it is possible that future studies will indicate that tibolone offers some protection against breast cancer. In this monkey trial, tibolone did not stimulate endometrial or mammary gland proliferation.

Clarkson et al suggest that the neutral effect of tibolone on atherosclerosis does not preclude some beneficial effect in women from the 3α-hydroxy and 3β-hydroxy metabolites, in that the decrease in HDL-cholesterol was greater than that observed in women and the increase in LDL-cholesterol observed in this monkey

trial is not seen in women. In treadmill experiments, tibolone reduces the signs of ischemia and prolongs the time to angina in a fashion similar to estrogen.[8] Tibolone also has a beneficial effect in short-term studies on insulin resistance in normal women and in women with noninsulin-dependent diabetes mellitus.[9,10] Tibolone has no effect on blood pressure.[11]

The results in the unopposed estrogen and the combined estrogen-medroxyprogesterone acetate groups are especially noteworthy, because this laboratory previously reported (in a frequently cited report) that the daily presence of medroxyprogesterone acetate attenuates the ability of conjugated equine estrogens to inhibit the development of atherosclerosis. (Adams MR, et al, *Arterioscler Thromb Vasc Biol.* 1997;17:217-221). Clarkson et al suggest the difference in the 2 reports may be due to daily treatment (the 1997 report) and twice-daily treatment (the current report) with a lesser progestin effect. However, I personally asked Tom Clarkson regarding this important clinical issue. He replied that his new study was bigger and better, and he does not believe that the daily presence of medroxyprogesterone acetate blocks estrogenic action on the coronary arteries.

The reason this is an important clinical issue is because some have attributed the early increase in clinical cardiac events in the HERS trial to the presence of medroxyprogesterone acetate. This new monkey report plus the failure to detect a difference between the unopposed estrogen arm and the combined estrogen-medroxyprogesterone acetate arm in the ERA trial are strong arguments that medroxyprogesterone acetate need not be feared. Avoidance of its use because of a concern over its effect on the coronary arteries is not justified. ❖

References

1. Ginsburg J, et al. *Maturitas*. 1995;21:71-76.
2. Tang B, et al. *J Steroid Biochem Mol Biol*. 1993;45: 345-351.
3. Lippuner K, et al. *J Bone Miner Res*. 1997;12:806-812.
4. Thiébaud D, et al. *Climacteric*. 1998;1:202-210.
5. Rymer J, et al. *Maturitas*. 1994;18:127-133.
6. Nathorst-Böös J, Hammar M. *Maturitas*. 1997;26: 15-20.
7. Hammar M, et al. *Br J Obstet Gynaecol*. 1998;105: 904-911.
8. Lloyd GWL, et al. *Int J Clin Pract*. 1998;52:155-157.
9. Cagnacci A, et al. *J Clin Endocrinol Metab*. 1997;82: 251-253.
10. Prelevic GM, et al. *Maturitas*. 1998;28:271-276.
11. Feher MD, et al. *Br J Obstet Gynaecol*. 1996;103: 281-283.

Labor—To Wait or Not to Wait: To Push or Not to Push

ABSTRACT & COMMENTARY

Synopsis: *This study underscores the need to re-evaluate periodically any concept of obstetrical management, no matter how solid the underlying scientific foundation.*

Source: Rouse DJ, et al. *Obstet Gynecol*. 2001;98: 550-554.

Many guidelines have surfaced over the years to help practitioners manage labor. Some of these have evolved into solidly ingrained dicta drummed into obstetricians during their residency training. Rouse and associates recently tested the well-established concept that lack of progress in cervical dilatation for 2 hours during the active stage of labor was grounds for cesarean section.

They evaluated the labors of 501 consecutive patients whose lack of cervical progress in active labor required management according to a special protocol. Oxytocin was used to maintain at least 200 Montevideo units for at least 4 hours before C-section could be performed. During that time period, a section was only done for fetal distress and not for failure to progress.

They found that 38 patients did not make any progress for 2 hours despite adequate contractions, as defined above. Twenty-three of these women (61%) successfully delivered vaginally without any increase in neonatal morbidity. The only difference was in maternal morbidity, as indicated by a higher rate of endometritis or chorioamnionitis, mostly in nulliparas (7% and 17%). There were 3 cases of shoulder dystocia (13%), but none of these infants had any morbidity.

In the 501 patients managed with the oxytocin protocol, the median cervical change was 1.8 cm/h in multiparas and 1.3 cm/h in the nulliparous patients. Interestingly, the 5th percentile for all patients was 0.5 cm/h, a figure substantially below the 5th percentile of 1.2 cm/h in nulliparas and 1.5 cm/h in multiparas noted by Emanuel Friedman in his landmark study accomplished in the 1960s.[1]

COMMENT BY JOHN C. HOBBINS, MD

This study underscores the need to re-evaluate periodically any concept of obstetrical management, no matter how solid the underlying scientific foundation. On the surface, it seems ludicrous to say that labors in the

1960s were different than labors in the 2000s. However, Friedman's patients did not have epidurals and 84% of Rouse's patients did, a distinction that could have an effect on the length of labors. Also, none of Friedman's patients had oxytocin augmentation, while all of Rouse's patients had it because their labors were already progressing too slowly.

Actually it is surprising that we have been setting unrealistic goals that no longer apply to some of today's patients. The same could be said about the 2-hour limit for the second stage of labor. Recent studies show that many patients can deliver safely by extending the second stage of labor well beyond 2 hours after full cervical dilatation is attained. This also could be an epidural-related phenomenon.

Although cesarean section rates rose steadily through the 1980s, they have plateaued over the last 5 years. However, the cesarean rate is likely to soar again based on our reluctance to deliver breeches vaginally and the recent backlash against VBACs. Also, for a variety of reasons, patients of advanced maternal age tend to have much higher cesarean section rates, and the percentage of pregnant patients 35 years of age or older rose from 8.5% in 1987 to 12.6% in 1997. In some hospitals in California, 30% of laboring patients now are more than 35 years of age.

Certainly, we ought to give a little more time to the diminishing number of patients who not only want to, but can deliver vaginally.

On a tangential note, dealing in this publication with labor allows the opportunity to touch upon another common concept that can be counterproductive. Fortunately, it is well accepted that initiating maternal pushing prior to complete cervical dilatation is a bad idea. However, it seems that attaining full dilatation now represents an immediate license to push. Although the idea behind this practice has been to shorten the second stage of labor, and perhaps to diminish the total amount of patient discomfort, there is little evidence to support this concept, especially where epidurals are used.

In fact, 2 recent studies have yielded important information regarding the management of second stage of labor. One randomized clinical trial involving more than 1800 patients demonstrated that although the second stage of labor was lengthened by an average of 64 minutes when patients were interdicted from pushing for 2 hours (unless they had an urge to push), the overall time of pushing was significantly less in the delayed pushing group (68 vs 175 mins). Also, there were fewer "difficult" deliveries in the delayed pushers.[2]

The other smaller randomized study (153 patients) showed no difference in length of second stage, rate of descent, or neonatal morbidity when patients delayed their pushing efforts for 1 hour.[3]

The point here is that the uterus generally does a reasonable job of accomplishing descent through the pelvis without immediate help. Delaying pushing for at least 1 hour will result in less time pushing (resulting in less exhaustion) and possibly fewer difficult deliveries without appreciable lengthening of the second stage or increase in morbidity.

Although pelvic floor abnormalities have been possibly associated with length of second stage, there are no available data dealing with time spent during passive descent vs. time pushing. During maternal pushing, the musculature of the pelvic floor actually contracts, a phenomenon that would predispose to later problems. Therefore, theoretically pelvic floor abnormalities might be more related to length of time pushing rather than the length of the second stage. ❖

References

1. Friedman E, Sachtleben M. *Am J Obstet Gynecol*. 1965;93:522-529.
2. Fraser WB, et al. *Am J Obstet Gynecol*. 2000;182: 1165-1172.
3. Mayberry LJ, et al. *J Perinatol*. 1999;19(1):26-30.

Clinical Features and Risk of Recurrence among Patients with Vaginal Intraepithelial Neoplasia

ABSTRACT & COMMENTARY

Synopsis: *Many patients with vaginal intraepithelial neoplasia have recurrence following treatment.*

Source: Dodge JA, et al. *Gynecol Oncol*. 2001;83: 363-369.

Primary neoplasia of the vaginal epithelium is an uncommon condition. Both vaginal intraepithelium neoplasia (VAIN) and invasive cancer occur infrequently in the United States. However, most studies of this condition have been limited to small series. Dodge and colleagues performed a retrospective chart review of all cases that occurred at their institution between 1989 and 2000. The pathology from each case was reviewed to be certain that the original diagnosis was correct. After this review, their series consisted of 121 patients

with any grade of VAIN. The charts of these patients were reviewed and a large number of variables were collected including demographic information, grade of VAIN, location of VAIN, treatment type, and recurrence. Unfortunately, Dodge et al only required a follow-up of 7 months and 1 post-treatment Pap smear to be included in the study. While they state this represents a longer follow-up than other studies, it is still short. Dodge et al mention this as one of the weaknesses of their study.

Of the 121 patients, 33% had VAIN I, 46% VAIN II, and 21% VAIN III. The mean age of the patients was 35 years (± 17 years). Almost all the patients had colposcopy and directed biopsies, but 8 patients had biopsy of a suspicious lesion seen with the naked eye. Nearly 80% of the lesions were located in the upper third of the vagina and 61% of the lesions were multifocal. In this series, 28 women had a prior hysterectomy.

Twenty percent of the patients had follow-up cytology only, 19% were treated with 5 fluorouracil (5-FU), 48% were treated with CO_2 laser, and 13% with partial vaginectomy.

None of the 13 patients treated with partial vaginectomy had a recurrence of their lesion. In contrast, 38% of those treated with CO_2 laser and 59% of those treated with 5-FU had recurrence.

Two patients developed invasive vaginal cancer. Both patients had multifocal lesions and both were treated with 5-FU. One had previously had a hysterectomy for CIN III and also had VIN III. The length of time from first diagnosis of VAIN to the development of vaginal cancer was 54 months and 24 months in these 2 patients.

Statistical analysis was able to identify 2 factors that predicted recurrence of VAIN: multifocality and method of treatment. Interestingly, age, smoking, HRT use, grade of VAIN, location of VAIN, and association with either CIN or VIN were not predictive of recurrence.

COMMENT BY KENNETH L. NOLLER, MD

I have always thought that VAIN is an interesting condition. It has not been well studied because it is relatively rare. This study is interesting, mostly because it reports one of the larger series of patients with VAIN in the literature. However, there is virtually no new information in the article. Dodge et al found that VAIN is associated with CIN and VIN, that 5-FU is a terrible treatment for the condition, that CO_2 laser has many recurrences, and surgical excision has the fewest. Multifocal lesions are harder to cure than unifocal, and most VAIN occurs in the upper vagina. All of these facts have been documented in prior, smaller studies.

In every article I read there was always some information that was not supplied by the researchers that I wish I knew. Dodge et al briefly mention the 2 patients that developed invasive cancer but provide little detail. I would be most interested in knowing how many women with VAIN I and no history of CIN or VIN had progression of disease. I strongly suspect that it is rare and that most lesions will spontaneously disappear. It would have been nice to have had that information reported since this is a relatively large series.

I also would have liked to have had more information on the 2 patients who developed invasive cancer. While one patient was described as previously having CIN III and VIN III, it is not clear whether she had VAIN I or VAIN II on initial presentation. Virtually no information is given about the past history of the other patient. Nor is there any information provided concerning the immune status of these patients.

Finally, it is clear that there is no place for the use of 5-FU in the treatment of VAIN. Indeed, in my opinion, there is no longer any indication for the use of 5-FU anywhere in the lower genital tract for intraepithelial lesions. ❖

Special Feature

The Phantom hCG Phenomenon

By David M. Gershenson, MD

The issue of the false-positive human chorionic gonadotropin (hCG), or the so-called "phantom hCG," has received increasing media and scientific attention and scrutiny over the past several months. The Society of Gynecologic Oncologists and the Diagnostics Division of Abbott Laboratories have recently issued alerts for physicians regarding the pitfalls of this phenomenon.

There is really nothing new about the phenomenon of a falsely positive hCG result. For several years, we have known about the fact that high levels of serum luteinizing hormone (LH) in menopausal patients may cross-react with hCG radioimmunoassays, giving a falsely abnormal value of hCG in the range of 5-10 mIU/mL. In such instances, oral contraceptives could be used to suppress the LH and thus eliminate concern about such a slightly elevated hCG. However, media coverage of

recent multimillion dollar lawsuits has heightened our awareness of this most recent twist on the subject.

Laurence Cole, a PhD at Yale at the time, was really the scientist responsible for highlighting and describing in detail the phenomenon of phantom hCG in 1998.[1] Prior to this time, Dr. Cole and others had published scattered case reports on the subject. In his 1998 report, Dr. Cole described 3 cases in which phantom hCG occurred. In the first, a 26-year-old woman was diagnosed with gestational trophoblastic disease following a dilatation and currettage (D&C) for a miscarriage. She had low levels of hCG in the range of 49-89 IU/L. Imaging studies were negative. She subsequently received chemotherapy and underwent hysterectomy for persistent elevations of hCG. Later, the diagnosis of phantom hCG was made, and therapy was discontinued. In the second case, a 28-year-old woman with a serum hCG of 69 IU/L and no fetal sac on sonogram underwent D&C and laparoscopy for a suspected ectopic pregnancy. No ectopic pregnancy was identified, and subsequent studies confirmed phantom hCG. In the third case, a 24-year-old woman with a serum hCG of 117 IU/L, diaphragmatic pain, and nausea, was diagnosed as having an early miscarriage. Because of persistence of abnormal hCG levels in the range of 45-135 IU/L over a 4-month period, the diagnosis of gestational trophoblastic disease was made. Imaging studies were negative, and the patient underwent D&C and subsequent chemotherapy. Studies later confirmed the diagnosis of phantom hCG.

Until the recent news stories of a malpractice suit based on misdiagnosis and unnecessary treatment of a woman with phantom hCG emerged, however, even gynecologic oncologists and obstetrician-gynecologists paid little attention to Dr. Cole's warning. Based on the recent flurry of headlines and alerts, we now better understand the phenomenon of phantom hCG. Phantom hCG appears to be a substance in blood that interferes with the hCG immunoassay. These interfering substances may represent heterophilic antibodies, human antimouse antibodies (HAMA), or other human antibodies to rabbit, goat, or sheep immunoglobulin, nonspecific protein binding, or hCG-like substances. Because the antibodies are large glycoproteins, they are not excreted in urine in any significant quantities. Therefore, if the phantom hCG phenomenon is suspected, it may be diagnosed by the absence of urinary hCG. In addition, a repeated hCG test using a different immunoassay platform usually reveals a normal hCG value. Dr. Cole also pointed out that serial dilutions of samples that contain interfering substances rather than true hCG give nonlinear results.

More recent reports in the literature include those of 12 patients who were incorrectly diagnosed with gestational trophoblastic disease because of phantom hCG (5 suffered surgical loss of reproductive potential, and 6 received unnecessary chemotherapy),[2] and another of 2 patients diagnosed with phantom hCG (one of whom received unnecessary chemotherapy and the other of whom was correctly diagnosed without unnecessary treatment).[3] This latter article was accompanied by a nice editorial authored by Charles B. Hammond, President-Elect of the American College of Obstetricians and Gynecologists.[4]

Phantom hCG is clearly a diagnosis that must be suspected before it can be made. As obstetrician-gynecologists or gynecologic oncologists, we are particularly vulnerable to falling prey to this diagnostic error since we are the physicians who generally treat pregnancy-related conditions, such as ectopic pregnancy and gestational trophoblastic disease. Furthermore, the initial diagnosis of such conditions may lead to surgical or chemotherapeutic treatment without a histopathologic diagnosis. Therefore, one should consider the diagnosis of phantom hCG in any patient who has hCG elevations in the lower range and a working diagnosis of ectopic pregnancy or gestational trophoblastic disease. In suspected cases of phantom hCG, it would behoove the attending physician to consider performing both a urinary hCG assay and another type of serum hCG assay in a reference laboratory prior to initiating therapy, thereby avoiding a potentially disastrous situation for the patient and the risk of liability for the physician. ❖

References

1. Cole LA. *Gynecol Oncol*. 1998;71:325-329.
2. Rotmensch S, Cole LA. *Lancet*. 2000;355:712-715.
3. Olsen TG, et al. *Obstet Gynecol*. 2001;98:843-845.
4. Hammond CB. *Obstet Gynecol*. 2001:98;719-720.

CME Questions

1. Which one of the following statements is true?

a. Tamoxifen use by women at high risk for breast cancer was associated with a reduction in the incidence of breast cancer when compared to placebo.

b. Tamoxifen use is clearly indicated for use in women with the BRCA2 mutation.

c. Tamoxifen use may be harmful for use in women with the BRCA1 mutation.

d. In vitro breast cancer cell cultures are very likely to tell us the exact mechanisms by which tamoxifen acts on breast tissue in vivo.

e. On the basis of the present data, women with BRCA1 mutations should be counseled to discontinue the use of tamoxifen.

2. **The following statements regarding tibolone are true *except*:**
   a. Tibolone has both estrogenic and progestational/androgenic actions on the cardiovascular system.
   b. The endometrium converts tibolone only to a progestational/androgenic metabolite.
   c. The daily presence of medroxyprogesterone acetate does not prevent estrogen's ability to reduce atherosclerosis.
   d. A randomized trial in monkeys indicates that tibolone and estrogen are comparable in their effects on the coronary arteries.

3. **Which one of the following methods of treatment of vaginal intraepithelial neoplasia (VAIN) resulted in the fewest number of cases with persistent/recurrence of the disease?**
   a. Repeat Pap smears only
   b. 5-fluorouracil topical cream
   c. CO_2 laser ablation
   d. Surgical excision

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Last year, as a test, we at *OB/GYN Clinical Alert* inserted *Ob-Gyn Coding Alert* into several issues. Response to this monthly advisor for ethically optimizing coding reimbursement published by The Coding Institute was overwhelmingly positive. Accordingly, we are bringing this extra feature back to our pages. Look for it each month, beginning with this issue.

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Hormone Therapy and In-Hospital Survival after MI in Postmenopausal Women

A supplement to *OB/GYN Clinical Alert*, January 2002 — published by *The Coding Institute*

OB-GYN CODING ALERT

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

AAPC Approved

Coding Q & A:

Get Expert Advice to Your Most Challenging Ob-Gyn Questions

Vaginal Hysterectomy

Question: *My physician did a vaginal hysterectomy (58260) and a combined anteroposterior repair (57260). During the same session she assisted a gyn/urologist in a paravaginal repair (57284) culdoplasty, which the physician says is the same as a enterocele and a tension-free vaginal tape (57288). How should I code for my surgeon's services?*

Nebraska Subscriber

Answer: Paravaginal defect repair (57284, *paravaginal defect repair [including repair of cystocele, stress urinary incontinence, and/or incomplete vaginal prolapse]*) is not the same as an enterocele repair with tension-free vaginal tape, but rather is an extensive procedure that corrects for multiple tissue weaknesses. This surgery can't be coded correctly without seeing the operative report because one of the procedures your surgeon wants to bill (the anterior repair) is included in the paravaginal defect repair done by the urologist.

Review the operative note for both procedures to see what has been documented.

Your physician can bill for the vaginal hysterectomy and posterior repair (if this is documented) with 58260 (*vaginal hysterectomy*) and 57240-51 (*posterior colporrhaphy, repair of cystocele with or without repair of urethrocele, -multiple procedures*) and report assisting at the paravaginal repair (57284-80, ... *assistant surgeon*) if this was not a Medicare patient.

Medicare will not allow a surgeon who is already billing as a primary surgeon to bill also as an assistant at the same operative session.

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Pap Billing

Question: *One of my physicians told me to bill 88141 with 88164. We send our Pap collections to a pathology lab where they are read. Can I bill for both of these codes?*

Maine Subscriber

Answer: Code 88141 (*cytopathology, cervical or vaginal [any reporting system]; requiring interpretation by physician [list separately in addition to code for technical service]*) is used by the pathologist who interprets the slide, not by the physician who ordered it. Reviewing the Pap results is part of the medical decision-making during the E/M service and is not billable separately.

Code 88164 (*cytopathology, slides, cervical or vaginal [the Bethesda system]; manual screening under physician supervision*) is a billable test service on the same day as the E/M or other service, but only if you have a CLIA certificate that permits you to bill for a lab service that is defined as complex, or if you are billing on behalf of the laboratory for this interpretation. In the latter case, you could bill for both of these codes, but you need to add modifier -90 (*reference [outside] laboratory*) to indicate that a reference lab performed the service. You should note, however, that Medicare would not allow you to bill in this fashion.

If you bill for the collection and handling of the specimen for a non-Medicare patient and use these codes, the correct code is 99000 (*handling and/or conveyance of specimen for transfer from the physician's office to a laboratory*). Some payers reimburse for the collection, and others include it as part of the E/M or preventive service.

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Billing for Antibiotics

Question: *We often administer oral antibiotics in addition to an E/M service. Does this change how we should bill the E/M service?*

Michigan Subscriber

Answer: The E/M service is billed the same, with the appropriate code for a new or returning patient (99201-99205, 99211-99215). Administering oral medication in your office to a pregnant patient who has the flu, for example, may be a problem because some states have laws against it due to licensing requirements. Many payers will not reimburse for the medication if dispensed from an office rather than a pharmacy. If your reason for administering the drugs in-house is merely to get the patient started on the antibiotics, you would be better off to shift the responsibility to the patient by giving her a prescription so she can get it filled and take the drugs on her own.

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Fetal Vesicocentesis

Question: *What is the code for fetal vesicocentesis, with a diagnosis of "abnormality of fetal urethra"?*

Texas Subscriber

Answer: The term "vesicocentesis" refers to aspiration of the bladder. The closest code in CPT is 51000 (*aspiration of bladder by needle*). There is no code specific to the fetus, but the procedure on a fetus requires some interesting manipulation, including possible ultrasonic guidance. If ultrasonic guidance is needed, you can add modifier -22 (*unusual procedural services*) with appropriate documentation of the extra work. But many payers may decide this procedure is experimental, so be prepared to appeal if the claim is denied.

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Transvaginal Ultrasound

Question: *How should I code a transvaginal ultrasound of the ovaries to measure follicles in a gonadotropin-stimulated cycle? I do one ultrasound when I initially see the patient and code it as 76856 and then code the follow-up transvaginal scans as 76857. The ICD-9 code is usually an infertility code such as 628.9.*

Minnesota Subscriber

Answer: You can use 76830 (*echography, transvaginal*) or 76856 (*echography, pelvic [nonobstetric], B-scan and/or real time with image documentation; complete*) to bill the initial ultrasound. The only difference between these two codes is that 76830 uses a vaginal transducer and 76856 uses an abdominal transducer. Imaging for both codes, according to the *ACOG Coding Manual* (*Ob/Gyn Coding Manual*: *Components of Correct Procedural Coding*, pp. 305-307), involves looking at the "uterus, tubes, ovaries and pelvic structures, as indicated." The approach determines which code to use.

For the follow-up to check for follicles, use 76857 (*echography, pelvic [nonobstetric], B-scan and/or real time with image documentation; limited or follow-up [e.g., for follicles]*), because it describes the procedure clearly. It does not matter whether the procedure is done transvaginally or abdominally. Medicare's fee schedule assigns the same number of RVUs for both 76830 and 76856 (2.62 RVUs), and there is no advantage to using one code over the other.

— Answers provided by ***Melanie Witt, RN, CPC, MA,*** *an independent coding consultant and ob/gyn coding expert based in Fredericksburg, Va.* ❑

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