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A monthly update of developments in female reproductive medicine

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High-Risk of Cerebral Vein Thrombosis in Prothrombin Gene Mutation Carriers and in Oral Contraceptive Users

ABSTRACT & COMMENTARY

The two most common causes of familial thrombophilia are mutations in the genes for factor V and prothrombin. These mutations are known to predispose to deep vein thrombosis of the lower extremities. In this study, Martinelli and colleagues sought to determine if these familial thrombophilias predisposed to cerebral vein thrombosis. The mortality of cerebral vein thrombosis is as high as 30%. Martinelli et al compared the prevalence of genetic and nongenetic risk factors in 40 patients with cerebral vein thrombosis, 80 patients with deep vein thrombosis of the lower extremities, and 120 healthy controls. The controls were matched to the patients for sex, age, geographic region, and level of education. The prevalence of the prothrombin gene mutation was higher in patients with cerebral vein thrombosis (20%) than in controls (3%), odds ratio 10.2 (95 confidence interval 2.3-31.0) and comparable to that of patients with deep vein thrombosis (18 %). Similar results were obtained for factor V gene mutation. Oral contraceptive use was more frequent among women with cerebral vein thrombosis (96%) than among control women (32%), odds ratio 22.1 (5.9-84.2). Women taking oral contraceptives who had a prothrombin gene mutation (7 patients and 1 control) had an odds ratio of 149.3 (31-711). The mean age of the women with cerebral vein thrombosis was 30 years and, for lower extremity DVT, also 30 years. (Martinelli I, et al. *N Engl J Med* 1998;338:1793-1797.)

COMMENT BY SARAH L. BERGA, MD

My companion article in the October 1998 issue of *OB/GYN Clinical Alert* reviews the recent study demonstrating that oral contraceptive use was found to protect women with the BRCA1 or BRCA2 mutation from ovarian cancer. It provides good news about oral contraceptives. On the other hand, these findings about oral contraceptive use and the risk of thrombosis sound a caution-

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INSIDE

ary note. More importantly, the articles demonstrate the emergence of molecular medicine as a tool for individualizing therapy. It may not yet be worthwhile or appropriate to genotype our patients as part of medical decision-making. However, as molecular epidemiology clarifies individual risk and as genotyping technologies advance, sooner or later there will come a time when it will be both feasible and worthwhile to genotype. When that intersection will occur depends on a number of factors, including the acceptance by society in general (and insurers in particular) that having an abnormal gene is not a "flaw" for which the individual must "pay," but a vulnerability or predisposition that must be taken into account when making a rational medical decision. Further, at the present time, physicians and pharmaceutical companies are often held liable for "bad" outcomes that are not knowable and, therefore, not preventable. Genotyping could help to lessen this liability.

The accompanying editorial (Bertina RM, Rosendaal FR. *N Engl J Med* 1998;338:1840-1841) also makes some important points. The proportion of carriers of factor V Leiden in the white population ranges from 2-15%. Heterozygotes have a seven-fold risk of DVT and homozygotes an 80-fold increase. All alleles are thought to derive from a common ancestor. The prevalence of prothrombin mutation is 0.7-4% of the white population and is rare in nonwhites. Oral contraceptives also change the balance between hemostatic and fibrinolytic components of the blood and are an important cause of nongenetic thrombophilia. This study suggests that oral contraceptive use in women with familial thrombophilia is hazardous, but neither group of authors called for routine screening of women contemplating oral contraceptive use. Since large-scale screening is not currently feasible, the next best step would be to design a less thrombogenic oral contraceptive. This makes more sense than screening, anyway, because oral contraceptives increase the risk of thrombosis even in women without familial thrombophilia. One strategy might be to avoid the use of ethinyl estradiol. Another strategy might be to nonorally deliver ethinyl estradiol in combination with a progestin. ❖

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Effect of Pregnancy on Multiple Sclerosis

ABSTRACT & COMMENTARY

Synopsis: *The rate of relapse in women with multiple sclerosis declines during pregnancy—most markedly in the third trimester.*

Source: Confavreux C, et al. *N Engl J Med* 1998;339: 285-291.

To determine the effect of pregnancy on the occurrence of relapse and disease progression in young women with multiple sclerosis (MS), investigators in 12 European countries (the Pregnancy in Multiple Sclerosis [PRIMS] group) studied 254 women during 269 pregnancies. The rate of relapse during the year before pregnancy, during each trimester of pregnancy, and for up to one year after delivery was determined. Short courses of glucocorticoids were the only treatment allowed during gestation.

Overall, pregnancy outcome in women with MS was good with no increase in perinatal deaths, preterm deliveries, or fetal malformations. In the study group of 227 first pregnancies, the rate of relapse in the first and second trimesters of pregnancy (0.5 relapses per woman per year and 0.6 relapses per woman per year, respectively) was no different from the rate of relapse in the year prior to the pregnancy (0.7 relapses per woman per year). Importantly, the rate of relapse during the last trimester of pregnancy was significantly lower (0.2 relapses per woman per year). In the first

three months after delivery, the rate of relapse rose significantly to 1.2 relapses per woman per year but, for the remainder of the first year, postpartum was no different from that prior to gestation. Epidural analgesia did not increase the risk of relapse after delivery while, in the 122 women who breast-fed their infants, the rate of relapse was significantly lower.

Confavreux and colleagues conclude that the rate of relapse in women with multiple sclerosis declines during pregnancy, most markedly in the third trimester. Relapses are more common during the first three months postpartum. Breast-feeding may reduce the risk of relapse, while epidural analgesia has no effect.

COMMENT BY STEVEN G. GABBE, MD

This important prospective study provides information that will be of great help in counseling young people with multiple sclerosis. This disorder, characterized by inflammation, demyelination, and axonal damage in the central nervous system, is twice as common in women as men. That the likelihood of relapse was not increased in pregnancy and was not altered by the use of epidural analgesia is reassuring. The rate of relapse did increase in the first three months postpartum—indicating a need for closer follow-up and prophylactic treatment soon after delivery. Breast-feeding appears to have a beneficial effect on the rate of relapse and can be encouraged in these patients. The beneficial effect of pregnancy seen in multiple sclerosis and rheumatoid arthritis is likely due to a relative increase in anti-inflammatory helper T cells as compared to pro-inflammatory helper T cells. This change is reversed in the postpartum period. ❖

Postmenopausal Hormone Therapy and the Risk of Ovarian Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *A meta-analysis of observational studies concludes that long-term postmenopausal hormone therapy slightly increases the risk of ovarian carcinoma.*

Source: Garg PP, et al. *Obstet Gynecol* 1998;92: 472-479.

Garg and associates performed a meta-analysis, examining the relationship between postmenopausal hormone therapy and the risk of epithelial ovarian carcinoma. After identifying 327 published citations, seven articles representing 12 analyses of 21 individual studies were included in this meta-analysis. The final conclusion indicated a relative risk of 1.14 (CI = 1.04-1.24) for developing invasive or borderline ovarian cancer among ever-users of postmenopausal hormone therapy. The relationship of invasive ovarian cancer with increasing years of hormone therapy use was derived from data from six studies. Among women who used hormone therapy for more than 10 years, the final relative risk for the development of invasive cancer was 1.27 (CI = 1/00-1.61). Garg et al conclude that the use of postmenopausal hormone therapy, especially for more than 10 years, is associated with an increased risk of developing invasive epithelial ovarian carcinoma.

COMMENT BY LEON SPEROFF, MD

In my opinion, this meta-analysis illustrates everything that is wrong with the application of this technique to observational studies. Meta-analysis is a technique developed to bring together small, randomized clinical trials in the effort to achieve greater statistical power. When applied to case-control cohort studies, it is subject to the same confounding biases that are present in individual studies. An overall increased risk of 14% in ever-users of hormone therapy in epidemiologic terms is slight and cannot be expected to reflect greater reliability when derived from case-control studies (as in this meta-analysis).

The conclusion that a 27% increased risk is associated with long-term use (more than 10 years) of hormone therapy is based upon six observational studies with data including long-term use. This conclusion, with a C.I. of 1.00-1.61, was by definition not statistically significant. Examining the individual conclusions of each of the six studies reveals that only one of these six reported significant increase with long-term use. This was a report from The Nurses' Health Study in 1995 (Rodriguez, et al. *Am J Epidemiol* 1995;141:828-835) that found no significant increase in the relative risk of fatal ovarian cancer with the ever-use of postmenopausal hormone therapy. The link with long-term use achieved statistical significance with only 18 cases. Thus, the conclusion of this meta-analysis, regarding increased risk with increasing duration of use, is tenuous. Despite this, in the discussion of the meta-analysis, Garg et al imply that this is a risk that should be included in the clinician-patient dialog. I strongly disagree.

A paragraph in the discussion is an excellent example of epidemiologic thinking that is not helpful for clinicians and patients. In making an argument for estrogens

in the etiology of ovarian cancer, they cite the publication in the *New England Journal of Medicine* (Rossing, et al. *N Engl J Med* 1994;331:771-776), which concluded there was a two- to three-fold increase in the risk of developing ovarian cancer with the long-term use of clomiphene. They don't share with the reader the fact that this conclusion was based on five cases, and, not surprising, the confidence interval (1.5-82.3) was extremely wide, reflecting the imprecision of their conclusion because of the small number of cases. They further ignore subsequent studies that failed to confirm a link between clomiphene and ovarian cancer. It is precisely studies like the clomiphene study in which clinicians are justified in concluding that statistically significant epidemiologic studies with small numbers and imprecision probably have no clinical relevance.

In view of the controversy in the last few years regarding the appropriate use of meta-analysis, it is disappointing to me that our journals give credibility to conclusions of meta-analyses such as this one based upon weak observational data. I am repeatedly impressed that epidemiologists believe that all data can be presented to patients, allowing objective decision-making on the part of the patients. There are some studies that involve cancer that cannot be separated from the emotions that surround the fear of cancer, and when the studies are incredibly weak, it is better that they do not enter the clinical dialog. This meta-analysis is a prime example. ❖

Route of Delivery on Regression of Abnormal Cervical Cytologic Findings in the Postpartum Period

ABSTRACT & COMMENTARY

Synopsis: *Vaginal delivery results in a higher rate of spontaneous regression of HGSIL than Cesarean delivery.*

Source: Ahdoot D, et al. *Am J Obstet Gynecol* 1998; 178:1116-1120.

This study examines the effect of the route of delivery on regression of CIN in 138 patients who had complete demographic clinical and cytologic reports, and who participated in postpartum follow-up. Twenty-six of the women had a smear showing ASCUS, 53 had LGSIL, and 59 had HGSIL. The Cesarean section rate did not differ among these groups. Likewise, age, parity, and a history of smoking were not significantly different. These women represent only about one-third of all of the women referred to the clinics performing this study. Unfortunately, data were lacking for the remaining two-thirds of the group, and they were not included in the study. However, there was no evidence that any type of systematic bias was the cause for the lack of complete information.

There was no significant difference in the regression of those women with ASCUS or LGSIL smears when they were compared by the route of delivery. *(See Table.)* However, there was a significant increase in the regression rate among women who were delivered vaginally when compared to Cesarean delivery.

Ahdoot and associates review possible explanations for the observed difference in HGSIL regression. They theorize that changes in the local immune response as part of the reparative process following vaginal delivery might be the cause. Likewise, the cause might be that significant abrasion of the cervical epithelium occurs at the time of delivery.

Table

Postpartum Regression of CIN

		(%)	
	Vag	**CD**	**P**
ASCUS	70	50	0.6
LGSIL	64	64	1.0
HGSIL	60	0	0.0002

Adapted from Ahdoot, et al. Am J Obstet Gynecol 1998;178:1116-1120.

COMMENT BY KENNETH NOLLER, MD

The management of abnormal Pap smears in pregnancy is difficult. Even experienced colposcopists have trouble examining and properly classifying women with abnormal Pap smears during gestation. Most reported series have shown that there is a great likelihood of misdiagnosis in pregnancy, even with experience.

We all have noted that many women no longer have evidence of CIN following delivery. This has been reported many times in the literature. However, this current study appears to be the first that has compared vaginal to Cesarean delivery. In my view, it is not at all surprising that the those women who vaginally deliver had less persistence of disease than those who delivered abdominally. The abrasion of the cervical epithelium as a result of the fetus passing through the birth canal, as

well as the required postpartum repair process, would seem to make it likely that CIN might disappear following vaginal delivery.

It is also not surprising that there was no difference seen between vaginal and abdominal delivery among women with ASCUS and low-grade smears. The regression rate of HPV/mild dysplasia/CIN I is at least 50%, and perhaps is as high as 70% after 1-2 years of follow-up. Thus, so many lesions would spontaneously disappear that it is unlikely that a significant difference would be noted (even if it exists) unless the study was large. ❖

Evaluation of Routine Antepartum and Postpartum Blood Counts

ABSTRACT & COMMENTARY

Synopsis: *Obtaining routine postpartum blood counts may not be useful.*

Source: Ries A, et al. *J Reprod Med* 1998;43:581-585.

This retrospective study compared the admission and postpartum hematocrit determinations for a group of 770 women delivering on the authors' obstetrical service during a six-month period. In addition, the 28-week hematocrit results were compared to the admission results to determine whether a difference in platelet concentration was noted. Ries and colleagues stratified the differences in hemoglobin concentration by type of delivery and delivery complication.

Ries et al found that there was no significant difference between the platelet concentration at the 28-week determination and the admission count.

Postpartum hematocrit concentrations were lower than those at the time of admission. However, all of the women requiring transfusion would have been identified because of complications occurring during the delivery process. These complications included such things as placenta accreta, severe pre-eclampsia with thrombocytopenia, uterine inversion, postpartum hemorrhage, acute fatty liver, broad ligament hematoma, Cesarean hysterectomy, and amniotic fluid embolus.

Among women who did not need to be transfused, women undergoing spontaneous vaginal delivery had the smallest mean decrease in hematocrit concentration, and those women having vacuum extraction had a slightly larger decrease. Forceps deliveries accounted for larger decreases than Cesarean deliveries.

COMMENT BY KENNETH NOLLER, MD

This is another article that questions our "routine" practice. At many hospitals, a postpartum hemoglobin is obtained on the first post-delivery day. Ries et al rightly question whether that is a reasonable (i.e., important) determination. Based on their results, it does not seem to be.

This is not a surprising finding. Although there are occasional low hematocrits on the first postpartum day, virtually every anemia would have been expected based on some type of hemorrhage. Why then do many hospitals routinely order them? It would seem only to add expense without significant benefit. While one hematocrit determination is relatively inexpensive, there are 4 million deliveries in the United States each year, and considerable cost savings could be achieved if we could eliminate most of them. I am certainly planning to argue for cessation of this test as a routine at our hospital.

It is interesting that Ries et al also looked at platelet concentrations between 28 weeks and admission. Though they never so state in their paper, it is clear that an admission platelet concentration must be obtained before their anesthesia team will insert an epidural. I wonder how many other places also have this policy? That has not been a routine on the obstetrical services I have been involved with during the past two decades.

Although Ries et al did not do the study, I wonder how useful their routine 28-week blood count would prove to be if carefully scrutinized? ❖

LPA as a Potential Biomarker for Ovarian and Other Gynecologic Cancers

ABSTRACT & COMMENTARY

Synopsis: *Plasma LPA levels may represent a potential biomarker for ovarian cancer and other gynecologic cancers. However, these findings are preliminary and require confirmation in larger studies.*

Source: Xu Y, et al. *JAMA* 1998;280:719-723.

Lysophosphatidic acid (lpa) has been shown to stimulate proliferation of ovarian cancer cells

and is present in the ascitic fluid of patients with ovarian cancer. Xu and colleagues at the Cleveland Clinic measured total LPA levels in plasma samples from 48 patients with ovarian cancer, 36 women with other gynecologic cancers, 17 women with benign gynecologic diseases, 11 women with breast cancer, five women with leukemias, and 48 healthy controls. Patients in the ovarian cancer group had significantly higher plasma LPA levels (mean, 8.6 mmol/L; range, 1.0-43.1 mmol/L) compared with the healthy control group (mean, 0.6 mmol/L; range, < 0.1-6.3 mmol/L) ($P < 0.001$). Elevated plasma LPA levels were detected in nine of 10 patients with stage I ovarian cancer, 24 of 25 patients with stages II-IV ovarian cancer, and 14 of 14 patients with recurrent ovarian cancer. Of 36 patients with other gynecologic malignancies, 33 also showed higher LPA levels (mean, 14.9 mmol/L; range, < 0.1-63.2 mmol/L), compared with healthy controls ($P < 0.001$). Elevated plasma LPA levels were detected in five of 48 controls, in four of 17 patients with benign gynecologic diseases, and in no women with breast cancer or leukemia. In comparison, among a subset of patients with ovarian cancer, 28 of 47 had elevated CA 125 levels, including two of nine patients with stage I disease. Xu et al conclude that plasma LPA levels might represent a potential biomarker for ovarian cancer and other gynecologic cancers. However, these findings are preliminary and require confirmation in larger studies.

COMMENT BY DAVID M. GERSHENSON, MD

Epithelial ovarian cancer remains the most lethal gynecologic malignancy. There is no effective screening test for ovarian cancer, as evidenced by the fact that more than 70% of cases are diagnosed after the tumor has already spread beyond the ovary. Although serum CA 125 has been studied, its sensitivity and specificity are suboptimal. In addition, ultrasound lacks specificity—an estimated 40-100 surgeries are required to diagnose one ovarian cancer. Current strategies in the area of screening include algorithms that use both modalities, the use of multiple serum tumor markers, or the longitudinal study of serum CA 125. The findings of this preliminary report suggest that LPA may offer hope as a new marker that may be more sensitive than serum CA 125. The fact that nine of 10 patients with stage I ovarian cancer had elevated LPA levels is most impressive, considering that serum CA 125 is abnormal in only about 50% of stage I ovarian cancers. LPA also appears to have potential as a biomarker in other gynecologic malignancies. However, five of 48 healthy controls and four of 17 patients with benign gynecologic conditions also had elevated LPA levels. The reason for these false-positive findings is obscure. LPA appears to be one of the most promising markers to emerge in a long while. As Xu et al point out, much larger studies are needed to firmly establish its use and role, if any, in early detection of ovarian cancer, monitoring of therapy effects in women with gynecologic malignancies, and in post-treatment surveillance. ❖

Special Feature

Vulvar Intraepithelial Neoplasia

By Kenneth Noller, MD

During the past 20 years, i have had the opportunity to attend and teach well over 100 colposcopy/lower genital tract neoplasia courses. This has afforded me the opportunity to listen to the greatest minds in the field describe their research and approach to the evaluation and treatment of lower genital tract neoplasia. One of the most interesting areas covered in these courses is intraepithelial neoplasia of the vulva (VIN).

Unlike cervical intraepithelial neoplasia (CIN), much less is known about the natural history of VIN. The lesion was not recognized as early as cervical dysplasia and is rarer, so no large series of patients with VIN have been followed prospectively without therapy. Nonetheless, there is now a general consensus concerning the management of most patients with VIN. In many cases, the current management recommendations are not widely known.

VIN III is a Cancer Precursor

There is now no doubt that VIN III (carcinoma in situ) is a precursor to invasive cancer of the vulva. Enough cases of VIN III have been followed without treatment, and invasive cancer has developed to state definitively that VIN III always should be treated.

For some years, some investigators did not believe VIN III was a cancer precursor, especially in younger women. In retrospect, that position makes little sense. Virtually, no one would now leave VIN III untreated.

VIN I is not a Cancer Precursor

There are virtually no data published in the literature

that support the premise that VIN I (mild dysplasia of the vulva) is a precursor to invasive cancer. This fact, when presented at a colposcopy course, often surprises some members of the audience. Nonetheless, it is a fact. I have not heard a speaker at a national course for at least a decade support treatment for VIN I. VIN I should not be treated.

There is a difference between the diagnoses of VIN I and CIN I. While most of us do not favor treatment of CIN I unless it persists for two or more years or progresses to CIN II (something that happens in only about 30% of cases), there is general agreement that VIN I should not be treated regardless of persistence. The reason for this lies in the inaccuracy of the pathologic diagnosis of intraepithelial neoplasia of the vulva. On the cervix, basal cell hyperplasia and early nuclear atypia do not routinely occur spontaneously unless HPV infection has occurred. On the vulva, similar changes are called VIN I but are probably most often due to irritation, repair, or some unknown mechanism. The vulva is much more likely to be traumatized through normal activity and sexual intercourse than is the cervix. In addition, although HPV infection of the vulva is common, the virus does not seem to be able to transform the vulvar epithelium into a self-perpetuating neoplastic lesion as easily as it can change the cervical epithelium.

HPV of the Vulva?

Unlike the cervix, it is difficult to diagnose the presence of HPV infection on the vulva if clinically evident warts are not present. The presence of acetowhite epithelium is *not* a sensitive or specific predictor of the presence of HPV. Also, it has been shown that biopsies of the vulvar epithelium, which are interpreted by competent gynecologic pathologists as showing HPV infection, are often found not to contain HPV when the tissue samples are subjected to HPV-DNA testing. When a competent gynecologic pathologist sees koilocytic changes with nuclear atypia on a cervical biopsy and diagnoses HPV infection, there is almost always HPV-DNA present. That is not true with vulvar biopsies. Thus, HPV infection of the vulva is grossly over-diagnosed. Although the role of HPV-DNA testing in the presence of cervical disease is still open to debate concerning its usefulness, it may have a role in vulvar disease, primarily to rule out the presence of an HPV infection despite a biopsy showing HPV-type changes.

What to do about VIN II?

It is clear that VIN III should be treated and VIN I should be ignored. What about VIN II? The short answer is that no one knows for sure. No prospective studies have been performed. However, we do know that if VIN II is present, and even if it is a precursor to invasive vulvar cancer, it will likely be several decades before invasion occurs. On the vulva, transition from intraepithelial disease to invasive disease occurs at a glacial pace. There is certainly no reason why VIN II cannot be followed in a patient who is reliable. On the other hand, if a patient has a history of poor compliance with follow-up instructions or has immune suppression for any reason (transplantation, HIV, inherited), it might be appropriate to treat VIN II when it is discovered.

I would strongly encourage, though, that VIN II never be treated in a young woman (teenage-25 years). VIN II tends to regress in this age group and treatment often leads to vulvar deformity and sometimes dyspareunia. It is easy to cause more harm than good. ❖

References

1. Küpper V, et al. *J Reprod Med* 1997;42:140-144.
2. Jones RS, Rowan DM. *Obstet Gynecol* 1994;84: 741-745.
3. Haefner HK, et al. *Hum Pathol* 1995;26:147-154.
4. Wilkinson EJ, Stone IK. *Atlas of Vulvar Disease*, Baltimore, MD: Williams and Wilkins; 1995:101-110.

CME Questions

23. Which of the following is true?

a. It is a mistake not to screen women contemplating oral contraceptive use for familial thrombophilias.
b. The prevalence of prothrombin gene mutations is low in non-white populations.
c. In the absence of prothrombin gene mutations, oral contraceptive use does not increase the likelihood of cerebral vein thrombosis.
d. Cerebral vein thrombosis is a disease of elderly women.
e. Prothrombin gene mutation is a risk factor for cerebral vein thrombosis, but the factor V gene mutation is not.

24. Based on the data of the PRIMS study, the most likely time for an increase in the rate of relapse for pregnant women with multiple sclerosis is:

a. first trimester.
b. second trimester.
c. third trimester.
d. postpartum.

25. According to the article by Ahdoot et al, spontaneous regression of cervical neoplasia postpartum occurs most often in women whose initial prenatal Pap smear showed which of the following?

a. Benign cellular changes
b. ASCUS
c. LGSIL
d. HGSIL

26. Which of the following statements concerning VIN I is most accurate?

a. VIN I may progress to invasive cancer.
b. VIN I indicates the presence of HPV infection.
c. VIN I is best treated with CO_2 laser.
d. VIN I should not be treated.

27. Serum CA 125 is elevated in what percentage of women with stage I epithelial ovarian cancer?

a. 10%
b. 20%
c. 35%
d. 50%
e. 70%

28. The following statements are true of postmenopausal hormone therapy and the risk of epithelial ovarian carcinoma *except*:

a. All of the epidemiologic data regarding ovarian cancer and the use of hormone therapy are derived from observational case-control or cohort studies.
b. Meta-analysis is a technique that can avoid epidemiologic errors and biases.
c. The majority of data available in the studies thus far have not indicated an increased risk of ovarian cancer associated with postmenopausal hormone therapy.
d. There are no data available from randomized clinical trials regarding the risk of ovarian cancer and hormone therapy.

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(2) Return from News Agents	0	0
i. Total *(Sum of 15g, 15h(1), and 15h(2)*	2637	2678
Percent Paid and/or Requested Circulation *(15c / 15g × 100)*	99	99

16. This Statement of Ownership will be printed in the November issue of this publication. ☐ Check box if not required to publish.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Donald R. Johnston, Publisher — Date: 9/25/98

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 on or before October 1, annually. Keep a copy of the completed form for your records.
2. Include in items 10 and 11, in cases where the stockholder or security holder is a trustee, 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 box. Use blank sheets if more space is required.
3. Be sure to furnish all information called for in item 15, regarding circulation. Fee circulation must be shown in items 15d, e, and f.
4. If the publication had second-class 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 the first printed issue after October, if the publication is not published during October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be printed.
6. Item 17 must be signed.

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

PS Form **3526**, July 1995

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CME Test Scantron Form