

The Negative Predictive Value of 'Inadequate' Endometrial Biopsy in Diagnosing Endometrial Neoplasia

Oxgur H. Harmanli, Shermilla Shunmugham, Ting Shen,
Karen L. Houck, and Ashwin J. Chatwani

Department of Obstetrics and Gynecology, Department of Pathology, Temple University School of Medicine,
Philadelphia, Pennsylvania

J Gynecol Surg 2004;20:13–16

ABSTRACT

Between January 1976 and August 2001, endometrial samples from 87 women who underwent endometrial biopsy for abnormal uterine bleeding at the authors' institution were reported as "inadequate." The medical records of 76 women were suitable for review and were used to investigate the negative predictive value of inadequate endometrial specimens. Mean follow up was 26 months (range, 0–60 months). Follow-up management varied from observation to further diagnostic biopsy or ultrasound, or to treatment with hysteroscopy, dilation and curettage, or hysterectomy (Fig. 1). Fifty-five women were postmenopausal and 21 were premenopausal (mean age, 55 years). Follow-up tissue diagnoses were available for 37 women. In these patients, there was 1 histologic diagnosis of complex hyperplasia without atypia. Among the 38 women without follow-up tissue diagnoses, there were no reports of further bleeding.

EDITORIAL COMMENT

(This is a very simple, straightforward study showing that there is minimal risk of missing endometrial hyperplasia or cancer with an endometrial biopsy read as "inadequate tissue for diagnosis." The lack of tissue in the biopsy is almost always the result of very thin, atrophic endometrium, which would not be associated with hyperplasia or cancer. Because this goes along with our thinking, it is natural to support this conclusion, but we would add 2 caveats. The first caution is that inadequate tissue could also be the result of the fact that the endometrial cavity was not sampled with the biopsy. If a false passage was created or only the endocervix was sampled, the biopsy will naturally not reflect the situation in the endometrial cavity. However, the clinician will be warned that an abnormality still persists because bleeding will continue. The patient should always be advised to notify you if symptoms persist, and that is an

indication to proceed to the next level. This could be a transvaginal pelvic ultrasound if one has not yet been obtained or perhaps a dilation and curettage and hysteroscopy is indicated. Although I am not a big fan of the value of hysteroscopy in the evaluation of postmenopausal uterine bleeding, it is often helpful in identifying and treating uterine polyps. When ultrasound shows a thickened endometrial stripe and the endometrial biopsy shows atrophy or insufficient tissue, you can confidently predict an endometrial polyp.

The second caution is that this is a relatively small study. So, despite the fact that over 1300 endometrial biopsies were reviewed, only 87 were reported as "inadequate" and only 37 patients had additional tissue samples. A negative predictive value of 97.3% means that 2 to 3 women per 100 might actually have a lesion that was not diagnosed by the "inadequate" biopsy.

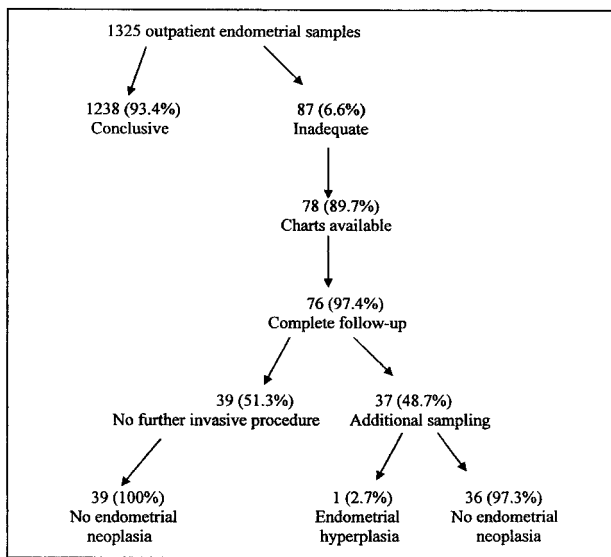


Fig. 1 The schematic view of the inadequate outpatient endometrial samples. Reproduced with permission. *J Gynecol Surg* 2004;20:13-16. Copyright ©2004, M. A. Liebert. All rights reserved.

As I said earlier, this is no big deal in my opinion because I believe they will continue to bleed, and their diagnosis will only be delayed 4 to 8 weeks, which should not affect their prognosis.

The clinician should also use good common sense. In an article we reviewed quite some time ago, Feldmen et al. identified age over 70, diabetes, and nulliparity as risk factors for endometrial cancer (*Obstet Gynecol Surv* 1995;50:779). Surprisingly, obesity was not a significant risk factor in this study, but many other studies have shown an increased risk of endometrial cancer in obese women. It is probably reasonable to start with an endometrial biopsy in the workup of higher-risk women with postmenopausal bleeding and use pelvic ultrasound to evaluate women at lower risk. Most experts would feel comfortable that significant hyperplasia or cancer has been ruled out if the endometrial stripe is less than 5 mm. A recent paper from Tel Aviv by Bruchim et al. suggests that this thickness might even be increased to 6 mm in women who are less than 15 years postmenopausal (*J Clin Ultrasound* 2004;32:219). Using either 5 or 6 mm as the cutoff, depending on the patient's time from menopause, would eliminate the need for 60% of endometrial biopsies according to these authors.—HWJ)

Expectant or Surgical Management of Miscarriage: A Qualitative Study

Jane Ogden and Cathy Maker

Department of General Medicine, Guys Kings and St. Thomas School of Medicine, London, U.K.

Br J Obstet Gynaecol 2004;111:463-467

ABSTRACT

Thirteen women who presented to the Early Pregnancy and Gynaecology Assessment Unit of the authors' institution with an incomplete miscarriage were offered the choice of surgical treatment or expectant management. The options were explained to the patients after ultrasound diagnosis. Five women each chose surgery and expectant management, and 3 tried expectant management but eventually underwent surgical treatment. An average of 5 weeks after the initial contact, the women were interviewed in depth about their experience. Women who chose expectant management expressed a desire to have a "natural" experience with natural healing, or they preferred to avoid surgery. Surgical treatment was chosen by women who were anxious to have the experience over with and who wanted to return to a normal life as quickly as possible. In both groups, some patients felt that they could have used more time and more information to make the treatment decision. Women in each group had similar experiences with bleeding and pain before coming to the early pregnancy unit, but women who opted for surgical management reported quick resolution of their

symptoms (Table 1). Women who had expectant management reported continued heavy bleeding with severe pain. Some did not feel prepared for the experience. Three patients who chose expectant management decided to undergo surgery when the pain and bleeding continued. Both groups reported strong emotional support from family and friends, but some in the expectant management group said that support diminished after several days. Most patients who underwent surgery reported good emotional support from the hospital personnel.

EDITORIAL COMMENT

(Several years ago, Creinin et al. reviewed the current management practices for early pregnancy failure (Obstet Gynecol Surv 2001;56:105). Although surgical evacuation is still widely preferred, expectant management and medical augmentation with prostaglandin analogs have had support in recent years. In evaluating the advantages and disadvantages of these management techniques, it is important to look carefully at the types of patients who are being managed. In general, suction curettage in the emergency department or in the operating room with a less than 24-hour hospitalization has proven to be an effective approach with minimal morbidity, which allows rapid return to normal activity. However, patients with an incomplete miscarriage (bleeding, cramping, and an open cervical os) will usually complete the passage of tissue on their own within 12 to 24 hours. Most of the clinical studies of early pregnancy failure have been done in Europe and include relatively few women with an incomplete miscarriage.

In a randomized, prospective study, de Waard et al. compared 58 women who were treated by curettage with 64 women who were managed expectantly (Hum Reprod 2003;17:2445). All women were seen initially with first-trimester bleeding and

an ultrasound showing fetal demise as evidenced by a gestational sac >15 mm in diameter without a measurable embryonic pole, an embryo without cardiac activity, or a gestational sac <15 mm in diameter with no growth over a 7-day interval. There were 4 women in each group with an incomplete miscarriage and retained products of conception >15 mm anteroposterior diameter in the uterus. Overall, less than half of the women evaluated for first-trimester bleeding met any of these criteria. Successful and complete evacuation of the uterus was achieved in 95% of the suction curettage group (3 patients required a second dilation and curettage), but spontaneous passage of the products of conception had occurred in only 47% of the expectant management group by 6 weeks. A larger, nonrandomized series had very similar results.

In another recent trial, Bargatze et al. randomized 104 women with early pregnancy failure (83) or incomplete miscarriage (21) to receive either expectant management or medical therapy with 3 tablets of intravaginal misoprostol (200 µg each) (Hum Reprod 2004;19:266). Women treated for an incomplete miscarriage did very well with either management plan: 100% for women treated with misoprostol and

TABLE 1 Themes and categories

Theme	Expectant management	Surgical management
Deciding on a treatment	Wanting more time to make decision, feeling ill qualified to make decision, wanting natural solution	Desire for quick resolution, return to normal
Experience	Fear of operations, wanting body to heal itself Pain Agony Feel like dying Bleeding Extensive Anxious that something's wrong Feeling unprepared, feeling misinformed, decision regret	Pain Subsided Return to normal Bleeding Subsided Return to normal
Social support	Family, friends shared experience Support declined over time	Hospital staff, surgery legitimized experience Wanted more emotional support

Reproduced with permission. Br J Obstet Gynecol 2004; 111: 463–467. Copyright ©2004, Blackwell Publishing. All rights reserved.

85.7% for those managed expectantly. However, if the diagnosis was early pregnancy failure with an intact gestational sac, then only 29% of the women followed expectantly aborted within 7 days, whereas 87% of the women treated with intravaginal misoprostol had emptied the uterus in a week. Two thirds of these patients actually required a second dose of vaginal misoprostol at 48 hours, and they averaged 4.5 outpatient visits during their management.

There has been little enthusiasm for expectant management in the United States. Perhaps

women, and their doctors, are more in a hurry and not eager to wait around for nature to take its course. However, the comments in the paper abstracted here suggest that women with early pregnancy failure who are followed expectantly often have considerable pain and prolonged bleeding. It is clear from this article that women who want to avoid surgery and/or "want to do it the natural way" need to have extensive counseling concerning bleeding and pain. They should have good family support and a patient gynecologist with nerves of steel.—HWJ)

Tetanus and Diphtheria Immunity Among Females in the United States: Are Recommendations Being Followed?

Deanna M. Kruszon-Moran, Geraldine M. McQuillan, and Susan Y. Chu

Division of Health and Nutrition Examination Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland; and the Office of the Director, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia

Am J Obstet Gynecol 2004;190:1070–1076

ABSTRACT

This study was conducted to determine the level of seropositivity to diphtheria and tetanus among women in the United States, and to investigate whether the recommendation of the Advisory Committee on Immunization Practices that adolescents and adults receive a booster vaccine for diphtheria and tetanus every 10 years after primary childhood immunization is practiced by the physicians who regularly care for women. Analyses were made using data from the third National Health and Nutrition Examination Survey (NHANES III; 1988–1994). This survey provided extensive demographic information gathered from personal interviews and clinical data collected by physical examinations performed in special mobile examination centers located throughout the United States. Among the 16,123 female participants, sera samples from 9411 females 6 years of age or older were available to test for antibodies to diphtheria and tetanus. Among all participants, 57% were seropositive for diphtheria, 64% for tetanus, and 48% for both. The percentages of women immune to diphtheria decreased with increasing age so that only 27% of women 60 years old or older had diphtheria seropositivity. The same trend was seen for tetanus, with only 23% of women having immunity at 60 years of age or older, but seropositivity to tetanus remained at 80% or greater until after 39 years of age. Immunity to both diphtheria and tetanus was greatest among young girls, age 6 to 11 years. No differences in diphtheria seropositivity were seen among different racial or ethnic groups (non-Hispanic white women, non-Hispanic black women, and Mexican Americans) in the youngest age interval, 6 to 11 years, or in the group aged 50 to 59 years. The highest seropositivity to diphtheria was seen in non-Hispanic white women aged 30 to 39 years; however, by age 50, non-Hispanic white women had the lowest immunity of all racial/ethnic groups. Mexican Americans were the only racial or ethnic group that had sufficient numbers to compare the seropositivity of women born in the United States with those born elsewhere. Mexican American women of childbearing age born outside the United States had significantly lower immunity to diphtheria than other racial or ethnic populations ($P < 0.01$ for all age groups except 40–49 years, which had a P value of 0.07). These patterns were repeated for tetanus seropositivity. The lowest immunity to tetanus was seen

in Mexican Americans aged 20 to 59 years who were born outside the United States ($P < 0.001$). An age-adjusted univariate analysis was conducted of possible variables related to seropositivity for both diphtheria and tetanus, including sociodemographic and healthcare access across each racial or ethnic group. Birth outside the United States continued to be a significant risk factor for lower immunity to diphtheria and tetanus for Mexican American women ($P < 0.001$ for both). Also, among Mexican American women, but not among other racial or ethnic groups, being at or above the poverty level and having access to regular health care were associated with higher levels of seropositivity. In general, immunity levels increased as levels of education increased, regardless of racial/ethnic group. For non-Hispanic white women and Mexican American women, nulliparous women had higher levels of seropositivity than those with 2 or more live births. Multivariate modeling adjusting for age, race/ethnicity, and foreign birth found higher education to have the highest association with higher seropositivity for all women and for non-Hispanic white women. Birth outside the United States, living below the poverty level, and low levels of education were predictors of low immunity to diphtheria and tetanus among Mexican American women. There were no unique predictive factors for non-Hispanic black women.

EDITORIAL COMMENT

(The Advisory Committee on Immunization Practices recommends a series of 3 combination diphtheria–tetanus–acellular pertussis vaccines in early childhood with booster injections of diphtheria and tetanus toxoid every 10 years. Despite this recommendation, the large national survey reported here indicates that only 50% of women over age 20 in the United States retain an immunity to diphtheria and only 58% to tetanus. Although women born in the United States had a significantly higher rate of immunity than foreign-born women, amount of education was the most significant demographic factor related to immunity. Is the lack of immunity to these rare infections important and should obstetrician–gynecologists be involved?

The Centers for Disease Control and Prevention reported only 2 cases of diphtheria and 37 cases of tetanus in 2001 (MMWR Morb Mortal Wkly Rep 2001;50:1). Tetanus usually occurs after an injury, but intravenous drug users represent an increasing number of cases. Most illnesses can be prevented by postinjury tetanus toxoid injection, but studies show that most patients did not seek medical attention for their skin wounds (MMWR Morb Mortal Wkly Rep 1998;47:1). Clinical illness and deaths are more common in patients over age 60, but fatalities do occur in younger patients. With the fre-

quency of international travel and the countries where our patients, friends, and family members visit in the line of duty or for humanitarian purposes, it is probably reasonable to take fairly simple precautions to maintain our immunity to tetanus and diphtheria.

Obstetrician–gynecologists are often the primary or even the sole healthcare provider for reproductive-aged women. Certainly, obstetricians routinely screen their pregnant patients for rubella and hepatitis B and administer vaccine postpartum. Surveys have shown that many clinicians also counsel their patients about other vaccine-preventable diseases such as influenza and pneumococcal pneumonia, but often fail to consider the less common tetanus or diphtheria. Schrag reported that although 90% of obstetrical–gynecologic practices screened their patients for rubella and hepatitis B, only approximately 50% offered immunization and only 10% offered all major immunizations (Obstet Gynecol 2003;101:704). It seems to me that it is reasonable to include a discussion of immunizations in the yearly examination, but whether a gynecologist should try to provide the immunizations or simply refer the patient depends on the type of practice and the availability of accessible and convenient access to vaccinations in the community.—HWJ)

Cisplatin as Initial Chemotherapy in Ovarian Carcinosarcomas: A Gynecologic Oncology Group Study

J. Tate Thigpen, John A. Blessing, Koen DeGeest, Katherine Y. Look, and Howard D. Homesley

Department of Medicine, University of Mississippi School of Medicine, Jackson, Mississippi; the Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, New York; the Department of Obstetrics and Gynecology, Rush Medical College, Chicago, Illinois; the Gynecologic Oncology Section, Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, Indiana; and Wake Forest School of Medicine and Brookview Research, Inc., Winston-Salem, North Carolina

Gynecol Oncol 2004;93:336-339

ABSTRACT

The Gynecology Oncology Group presents a series of 136 patients with carcinosarcoma of the ovary who were treated with 50 mg/m² cisplatin delivered in 3-week intervals. After each course of treatment, patients underwent reassessment. Treatment continued until disease progressed or toxicity became unacceptable. The maximum number of cycles received by any patient was 15. Six women did not meet the criteria for evaluation. Forty-four of the remaining 130 patients had measurable disease, and 86 could be evaluated only for disease progression and overall survival. Among the 44 patients with measurable responses, 1 woman had a complete response to treatment with cisplatin, and 8 patients (18%) had a partial response. Median survival time for these patients was 19.0 months. Ten patients (23%) had stable disease, and 25 (57%) had progressive disease. Among these women, median survival was 4.7 months. Median progression-free survival for all 44 patients was 5.2 months and median overall survival was 11.7 months. For the 86 women without measurable lesions, median survival was 15.8 months. Some nausea and vomiting was experienced by 81 patients, and grades 3 and 4 toxicity were seen in 3 and 4 patients, respectively. Forty-seven patients developed myelosuppression; 11 of these women had grade 3 neutropenia. No patient died of treatment.

EDITORIAL COMMENT

(Carcinosarcoma of the ovary is a rare tumor. This series of 136 patients is many times larger than any other previously reported treatment series. The fact that it took the Gynecologic Oncology Group 20 years to accumulate these patients indicates the rarity of these lesions and the difficulty of testing new chemotherapies, which could become yesterday's drugs or outdated doses before the study is finished. The response rate of approximately 20% to cisplatin is similar to the reported response rate for uterine carcinosarcomas. So in the future, we will probably extrapolate the results from the somewhat more common uterine sarcomas and use the same treatment plans for women with ovarian carcinosarcomas.

Primary ovarian carcinosarcomas are generally mixed mesodermal (or mesenchymal) tumors with endometrioid carcinoma plus a ma-

lignant sarcoma element. Similar to their uterine counterparts, the sarcomatous tissue could be homologous arising from normal ovarian tissue, usually stroma, or heterologous, which is foreign to the ovary such as cartilage, bone, or striated muscle. Prognosis for these lesions is very poor, and current opinion is that there is no difference in prognosis between the various cell types. In a recent review of the large, national Surveillance, Epidemiology, and End Results (SEER) database for the years 1988-1997, over 14,000 cases of ovarian cancer were reviewed (Barnholtz-Sloan, et al. *Gynecol Oncol* 2004;93: 506). Women with early-stage ovarian malignant, mixed mullerian tumors had a 30% higher risk of death than women with poorly differentiated epithelial ovarian cancers, and those with high-stage disease had a 60% greater risk of death. Median survival was only 13 months in

women with advanced disease, which is similar to the 11.7 months reported in the adjuvant treatment series reported here.

Because of the rarity of these tumors, it is difficult to identify prognostic factors, but stage could be significant. In a small series of 31 patients, Barakat et al. reported a median survival for 8 women with early-stage, completely resected disease of 105 months compared with only 9.5 months for the 23 patients with stage III or IV disease (Obstet Gynecol 1992; 80:660). There is no evidence that adjunctive

radiation therapy improves survival. Although the authors of this article suggest that the 20% response rate to cisplatin chemotherapy at 50 mg/m² every 3 weeks is evidence of activity, overall median survival rate for this series was not different than reported for other smaller series who were untreated or treated with other agents. Nevertheless, we will undoubtedly continue to use platinum-containing regimens for women with carcinosarcoma, but no significantly effective therapy has yet been demonstrated.—HWJ)

Lower-Category Benign Breast Disease and the Risk of Invasive Breast Cancer

Jiping Wang, Joseph R. Costantino, Elizabeth Tan-Chiu,
D. Lawrence Wickerham, Soonmyung Paik, and Norman Wolmark

National Surgical Breast and Bowel Project; the Department of Biostatistics, Graduate School of Public Health, Department of Surgical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania; the Department of Surgical Oncology, Department of Pathology, Allegheny General Hospital, Pittsburgh, Pennsylvania; and the Cancer Research Network, Plantation, Florida

J Natl Cancer Inst 2004;96:616–620

ABSTRACT

The Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project follows 11,307 healthy women who are at increased risk for breast cancer. The participants were randomly assigned to receive prophylactic tamoxifen or placebo for 5 years and to undergo regular follow-up studies. From this group, the authors have identified 1376 women who were diagnosed with benign breast disease, which had a pathologic classification of 1 or 2. These are the least serious in the College of American Pathologists classification of benign breast disease and include adenosis, ductal ectasia, fibroadenoma, fibrosis mastitis, mild hyperplasia without atypia, ordinary cysts, simple apocrine metaplasia, squamous metaplasia, moderate or florid hyperplasia without atypia, sclerosing adenosis, and solitary papilloma without coexistent atypical hyperplasia. In the group of 1376 women with lower-category benign breast disease (LC-BBD), 47 have been diagnosed with breast cancer, yielding an average annual breast cancer diagnosis rate of 7.20 per 1000 for these women. Among 9931 women in the breast cancer project who did not have LC-BBD, 291 developed breast cancer, resulting in an average annual rate of 4.40 per 1000. The relative risk for breast cancer in women with LC-BBD was 1.60 (95% confidence interval [CI], 1.17–2.19) compared with those without LC-BBD. Older women (over 50 years of age) had an annual rate of breast cancer of 8.46 per 1000 for those with LC-BBD and 4.28 per 1000 for those without LC-BBD (relative risk [RR], 1.95; 95% CI, 1.29–2.93). Younger women (under 50 years of age) with and without LC-BBD had average annual breast cancer rates per 1000 of 5.99 and 4.62, respectively (RR, 1.26; 95% CI, 0.78–2.05). Tamoxifen afforded women some protection against breast cancer. Among women with LC-BBD, those who took tamoxifen developed breast cancer at an annual rate of 6.30 per 1000 compared with 8.04 per 1000 for those who took placebo. Women without breast disease had annual rates of 3.52 per 1000 in the tamoxifen group and 5.43 per 1000 in the placebo group. The relative risk of breast cancer in the LC-BBD group was 1.46 (95% CI, 0.97–2.21) among women taking tamoxifen and 1.69 (95% CI, 1.05–2.73) for those taking placebo. A benign breast

cyst was the most common diagnosis in the LC-BBD group, accounting for half of all cases. The average annual rate of breast cancer for women with cysts was 8.07 per 1000 (adjusted RR, 1.6; 95% CI, 1.07–2.4).

EDITORIAL COMMENT

(Over the years, there have been a number of studies that have examined the risk of subsequent malignancy after a diagnosis of various types of “benign breast disease.” In a landmark study, DuPont and Page showed that the relative risk of developing invasive breast cancer increased 5.3-fold in women with atypical hyperplasia (N Engl J Med 1985;312:146). Since then, other large studies have helped us to understand the risks associated with benign cysts, sclerosing adenosis, fibroadenomas, and other lesions classified under the heading of benign breast disease. Using the results of those studies, the College of American Pathologists published a classification of benign breast diseases, which stratified the lesions into different risk categories as shown in Table 1 (Fitzgibbons, et al. Arch Pathol Lab Med 1998;122:1053).

The series reported here suggest there is an almost 2-fold increased risk of developing breast cancer in women who are diagnosed with 1 of the lower-category breast lesions after age 50. These results were largely the result of women with benign breast cysts, which was a common diagnosis in this study and was found to increase the risk of cancer

by 60%. Although this study reviewed over 11,000 women followed in the Breast Cancer Prevention Trial, there were only 47 patients with lower-category benign breast disease who went on to develop invasive breast cancer. So the authors caution that their observations need to be confirmed by larger studies with central pathology review.

What should we do as clinicians in the meantime? Oral tamoxifen at 20 mg per day has been shown to reduce the risk of breast cancer by approximately 50%. The lifetime risk of breast cancer can be quickly calculated using several risk factors, including prior breast biopsies, age, age at menarche and first pregnancy, and family history. “Gail model” risk assessment calculators are available from your Astra-Zeneca representative (manufacturers of Nolvadex-tamoxifen) or online at <http://bcra.nci.nih.gov/brc/q1.htm>. If the model calculates that a woman has a risk of greater than 1.7% of developing breast cancer within the next 5 years, most experts would recommend that she consider tamoxifen prophylaxis. There are risks of venous thrombosis and endometrial cancer associ-

TABLE 1 Categories of the College of American Pathologist classification of benign breast disease (2)

Pathologic category	Level of increased risk for invasive breast cancer	Pathologic types included in the category
1	No increase	Adenosis (other than sclerosing adenosis) Ductal ectasia Fibroadenoma without complex features Fibrosis Mastitis Mild hyperplasia without atypia Ordinary cysts (gross or microscopic) Simple apocrine metaplasia (no associated hyperplasia or adenosis) Squamous metaplasia
2	Slightly increased	Fibroadenoma with complex features Moderate or florid hyperplasia without atypia Sclerosing adenosis, Solitary papilloma without coexistent atypical hyperplasia
3	Moderately increased	Atypical ductal hyperplasia Atypical lobular hyperplasia
4	Markedly increased	Ductal carcinoma <i>in situ</i> Lobular carcinoma <i>in situ</i>

Reproduced with permission. J Natl Cancer Inst 2004; 96: 616–620. Copyright © 2004 Oxford University Press. All rights reserved.

ated with tamoxifen use so that the risks as well as the benefits need to be carefully evaluated, especially in women over age 50 in whom the risks of side effects are greater. Based on these new data for benign breast

cysts, it could be reasonable to recommend that such women also consider counseling from an expert in breast diseases to help make a decision about follow up and possible tamoxifen chemoprevention.—HWJ)

The Desire of Infertile Patients for Multiple Births

**Ginny L. Ryan, Sunny H. Zhang, Anuja Dokras, Craig H. Syrop, and
Bradley J. Van Voorhis**

University of Iowa Roy J. and Lucille A. Carver College of Medicine and University of Iowa Hospitals and Clinics, Iowa City, Iowa

Fertil Steril 2004;81:500–504

ABSTRACT

Despite the increased risks inherent in multiple births, patients do not always share their physicians' concerns. This prospective survey was carried out in 464 infertile women presenting for an initial visit. The goal was to determine the proportion of women who preferred a multiple to a singleton birth and how much these women knew about the attendant risks. The women were seen at an academic university hospital-based infertility center and a private general gynecology clinic. The 449 women who returned the questionnaire had a mean age of 31 years and were mostly well educated and from high-income families. Two thirds were nulliparous. The median duration of infertility was 33 months. A majority of women had previously seen another physician concerning their infertility. One in 5 women (20.3%) preferred twin,

triplet, or quadruplet pregnancies to a singleton pregnancy. Nearly 95% of these women reported twins as their first choice. Effective treatment, safety, affordability, and time to conception all were viewed as more important than avoiding a multiple birth. Most women did know that preterm delivery was more likely with twin birth, but fewer than half knew of the increased risks of infant death and cerebral palsy. After adjusting for maternal age, duration of infertility, clinic site, and knowledge about the risks of twin pregnancy, the only factors independently associated with a desire for multiple births were nulliparity and lower family income. A minority, but a significant minority, of infertile women desires multiple pregnancy. Patient education could well help to lower the incidence of twin and higher-order multiple pregnancies.

[Please see next abstract for Editor Comments.]

Parenting Stress in First-Time Mothers of Twins and Triplets Conceived After *in vitro* Fertilization

Cris Glazebrook, Charlotte Sheard, Sara Cox, Margret Oates, and George Ndukwe

Queens Medical Centre and the University of Nottingham, Nottingham, U.K.

Fertil Steril 2004;81:505–511

ABSTRACT

There is evidence that parenting twins adversely affects the mother's emotional well-being, and triplet births pose even more demands. This prospective cohort study examined parenting stress and psychosocial status 1 year postpartum in 129 women having a single naturally conceived birth, 95 with a single *in vitro* fertilization (IVF) birth and 36 with a twin or (in 5 instances) triplet IVF birth. Participants entered the study at 18 weeks gestation and were followed up 6 weeks and 12 months after giving birth. Both the General Health Questionnaire (GHQ)-12 and Parenting Stress Index Short Form were administered. Multiple IVF births were associated with higher total parental stress scores than women with natural pregnancies and also more child difficulty and more dysfunctional parent-child interaction. Compared with singleton IVF births, women with multiple IVF births had significantly higher scores for total parenting stress, and also more child difficulty and dysfunctional interaction. The singleton natural and IVF birth groups did not differ significantly in these respects. Similar findings were obtained after excluding triplet births. Abnormal total parenting stress scores at and above the 85th percentile were found in 22% of the multiple IVF birth group, 5% of women with a singleton IVF birth, and 9% of those who conceived naturally. Mothers with multiple IVF births were less likely to be working outside the home at follow up. Only 26% of women with singleton IV births reported having felt depressed in the year after giving birth, compared with 41% of women who conceived naturally and 47% of those with multiple IVF births. There were, however, no significant differences in the frequency of medical treatment for depression or in GHQ scores. These findings confirm reports that having a singleton IVF birth is not associated with increased parenting stress. Parenting more than 1 young infant is demanding, especially for an inexperienced mother. The women studied were generally in stable long-term relationships and were able to pay for fertility treatment. The effects of multiple births are probably greater in socially and psychologically disadvantaged families.

EDITORIAL COMMENT

(After the novelty and excitement of twins and higher multiple pregnancies, often in couples with a history of subfertility and emotionally and financially taxing experiences, fatigue, financial concerns, varying degrees of depression and disillusionment often set in. Combine that with the increased risk of premature labor and delivery, the increased costs associated with prolonged hospitalization for these premature babies, and the trend in several countries toward implanting no more than 1 or 2 embryos becomes understandable.

The desire by assisted reproductive technology (ART) programs to have higher pregnancy rates by implanting multiple embryos is understandable, but might not be in the best interests

of their patients or their offspring, emotionally and/or healthwise.

However, is there a subset of women or couples who actually would prefer to have a higher-order pregnancy, and, if so, are they adequately informed about the challenges of multiple pregnancies? The 2 articles I review here, and a related proposal by Dr. David Healy from Australia that also appears in the same issue of the journal (Fertil Steril 2004;81:512), address different facets of these questions.

In the article by Glazebrook et al., the authors investigated psychosocial and obstetric outcomes 1 year postpartum in first-time mothers who conceived after *in vitro* fertilization (IVF) and had a singleton, twin, or triplet pregnancy and

compared their findings with women with a naturally conceived singleton birth. They used a General Health Questionnaire and Parenting Stress Index to obtain their data. (One wonders whether they should also have had a fourth arm of the study in which a similar analysis of women who naturally conceived twins or triplets was performed, although adequate numbers of these women would be more time-consuming to obtain and might require studying women from more than 1 treatment unit.)

Similar to previous studies (Gibson FL, et al. *Fertil Steril* 2000;73:563; Hahn CS, Di Pietro JA. *Dev Psychol* 2001;37:37), they found that a singleton IVF birth was not associated with increased parenting stress. They also found that the majority of mothers in this group found the experience of motherhood very rewarding. In contrast, mothers with multiple IVF births had high levels of parenting stress. Their scores for total parenting stress, parent-child dysfunctional interaction, and perception of child difficulty were significantly greater than those of mothers with singleton IVF births and those with singletons conceived naturally. In addition, the women with multiple births who had undergone IVF were more likely than those with singleton births to report being depressed since the birth. The authors indicated that the percentage of mothers in the multiple IVF group who had General Health Care Questionnaire scores indicating a psychiatric disorder 1 year postpartum was similar to that in community surveys of postnatal mental health and is consistent with previous studies of mothers of twins and triplets in Australia where this study was performed. They concluded that the observation that mothers of twins and triplets in the present study did not differ from mothers with singleton births on the General Health Questionnaire score or score on the parental distress subscale of the Parenting Stress index reflected the demands of parenting rather than generalized emotional disturbance.

The authors also found that more than half of the mothers in the multiple IVF pregnancy group were not working outside the home at 1 year postpartum. They note that in addition to conferring financial advantages and independence and social status, employment also can be pro-

TECTIVE OF mothers' mental health. The disparity in employment status likely reflects the practical and economic difficulties in obtaining child care for 2 or more babies.

As might have been anticipated, medically, the babies in the multiple IVF group were more premature, had lower birth weights, spent more time in the newborn intensive-care unit, and were more likely to have medical complications.

The authors concluded that the demands on inexperienced mothers of parenting more than 1 infant are emphasized by their study, and although the couples could have been advised about the medical risks of multiple pregnancies, the potential social and psychologic implications could have been neglected.

In the other study, by Ryan et al., the authors sought to determine the proportion of subfertile women who prefer a multiple birth over a singleton birth and assessed the patient characteristics associated with this preference and, importantly, and as implied by the conclusions in the paper by Glazebrook et al., explored patients' knowledge about the risks of multiple births. They determined demographic characteristics, infertility history, desire for multiple births, knowledge of the risks of multiple births, and the goals of infertility evaluation and treatment using a 41-question survey.

They found that approximately 20% of women desired multiple pregnancies over singletons. Associated with this desire were nulliparity, lower family income, younger patient age, prior evaluation for infertility, longer duration of infertility, and, perhaps most importantly, lack of knowledge of the risks of twin pregnancies. They concluded that patient education could be an effective strategy for reducing the incidence of multiple pregnancy.

In the commentary by Healy (*ibid.*), he notes that the markedly increased morbidity and mortality associated with multiple pregnancies, and, by inference, the sociologic and psychologic consequences of pregnancy can be obviated by focusing on having a successful singleton birth at term. Like both Glazebrook et al. and Ryan et al., Healy feels that adequate education about the pitfalls of multiple births is essential. He points out that the educational information must

be at a level that patients can understand, and, as Ryan et al. also found, simple words should be used to convey the information. He recommends that infertile couples should be advised that twins are approximately 10 times more likely to be damaged by cerebral palsy and 3 times more likely to die than is a single baby.

I support the concept of taking the time to educate patients about the risks of multiple pregnancies as well as the details of the IVF procedures. Practitioners should provide this education without coloring it in any way because of their desires to have higher pregnancy rates by implanting multiple embryos.—RBJ)

Minimal Response of Circulating Lipids in Women With Polycystic Ovary Syndrome to Improvement in Insulin Sensitivity With Troglitazone

Richard S. Legro, Ricardo Azziz, David Ehrmann, Anita Gmerek Fereshetian, Mary O'Keefe, and Mahmoud N. Ghazzi for the PCOS/Troglitazone Study Group

Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey, Pennsylvania; the Department of Obstetrics and Gynecology, Cedars Sinai Hospital, Los Angeles, California; the Department of Medicine, University of Chicago Medical Center, Chicago, Illinois; and Pfizer Pharmaceutical Research, Ann Arbor, Michigan

J Clin Endocrinol Metab 2003;88:5137–5144

ABSTRACT

Women with polycystic ovary syndrome (PCOS) often are resistant to insulin, and the latter condition has been associated with dyslipidemia. The investigators examined the hypothesis that troglitazone (TGZ), an insulin-sensitizing drug, would improve dyslipidemia in these patients. A total of 398 women with PCOS were randomly assigned to receive placebo or TGZ in a dose of 150, 300, or 600 mg daily for 44 weeks. At the outset, 35% of women had a total cholesterol of 200 mg/dL or higher, 31% had a low-density lipoprotein cholesterol (LDL-C) of 130 mg/dL or higher, 15% had a high-density lipoprotein cholesterol (HDL-C) less than 35 mg/dL, and 16% had triglycerides exceeding 200 mg/dL. Lipid levels did not correlate closely with parameters of insulin action. None of the lipid levels responded significantly to the lowest dose of TGZ. There were favorable but not significant trends in HDL-C and LDL-C as well as a trend toward decreased triglycerides with the 300- and 600-mg doses of TGZ. This was the case for both intention-to-treat analysis and for those completing the study. Treatment effects were minimal even when only patients with baseline dyslipidemia were analyzed. Indices of insulin action, including an oral glucose tolerance test, were not substantially different in patients who responded to TGZ and those who did not respond. Dyslipidemia is present in many of these women with PCOS, but treatment with an insulin-sensitizing drug had minimal effects on circulating lipid levels.

EDITORIAL COMMENT

(During the past year in the *Survey*, I have been discussing articles related to various aspects of the metabolic syndrome. This syndrome, which includes obesity, dyslipidemia, in-

sulin resistance, and cardiovascular disease, is becoming more widely recognized by physicians and other caregivers. Because of its frequency and importance, in that it could precede

the development of type 2 diabetes, hypertension, and coronary artery disease, the Hormone Foundation (www.hormone.org), the public education affiliate of the Endocrine Society, is developing a comprehensive program on the components of the syndrome, and, in concert with the Endocrine Society, is mounting an extensive media and public education program on obesity.

Of course, components of the metabolic syndrome are also common findings in polycystic ovary syndrome (PCOS). Therefore, it was appropriate for Dr. Legro and his associates to assess the possible changes in circulating lipids in women with PCOS in response to increases in insulin sensitivity (decreased insulin resistance) using the insulin-sensitizing agent, troglitazone. (Dr. Legro recently prepared a review of insulin resistance and PCOS, which appeared in the February 2004 issue of the *Survey*.) Surprisingly, the response of circulating lipids to this treatment was not as robust as might have been anticipated.

They performed a multicenter, double-blind study with women who had PCOS and insulin resistance. The women were randomized to receive either a placebo or 1 of 3 doses of troglitazone (which has been removed subsequently from the U.S. market because of problems of liver disease). They quantified the response of circulating lipids and lipoproteins (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides (TTG) by treatment arm. Although this does not include all of the lipids involved in cardiovascular disease, they are the most commonly measured ones. They also assessed the influence of glycemic status on baseline levels and response to treatment. They found a high incidence of abnormal baseline lipid concentrations and responses to treatment using the definitions of the National Educational Program guidelines (total cholesterol ≥ 200 mg/dL; LDL-C, ≥ 130 mg/dL; HDL-C, < 35 mg/dL; and TTG > 200 mg/dL).

They found that at baseline, the parameters of insulin action were poor predictors of lipid concentrations. There was no significant response of any of the lipids measured to any of the doses of troglitazone. There were favorable trends,

which did not reach statistical significance, toward increased HDL-C and decreased LDL-C and TTG, in the 300- and 600-mg troglitazone dosage arms. Furthermore, there was a minimal treatment effect noted when they dissected out and separately assessed those women with abnormal baseline lipid levels.

Both Dr. Legro and his colleagues (Azziz R, et al. *J Clin Endocrinol Metab* 2001;86:1626) and others have demonstrated that hyperandrogenemia is reduced and the incidence of ovulation is increased when patients with PCOS use insulin-sensitizing agents. (Actually, the patients in the present study appear to be those in the study by Azziz et al. noted above) PCOS patients who are clomiphene-resistant also appear to become clomiphene-sensitive when insulin sensitivity is measured. Weight reduction in those patients who are overweight or obese also is beneficial in reducing insulin resistance and increasing ovulation, but in the present study, Dr. Legro et al. asked the subjects to follow a weight maintenance program to minimize the effects of weight loss on glycemia and lipid indices.

So why were improvements in the lipid responses to troglitazone not more robust? Although the definitive answers are not readily available, possibilities include: 1) perhaps other insulin-sensitizing agents such as metformin acting by different mechanisms could be more effective in this regard; 2) the study was terminated prematurely by the manufacturer when troglitazone was removed from the market. Therefore, there was a greater proportion than usual in the intent-to-treat group compared with the group that completed the entire study, and this could have influenced the results; 3) as Dr. Legro et al. comments in the "Discussion," the etiology of dyslipidemia in this population appears to be minimally influenced by the improvements in the parameters of glycemic action, which were seen in this group in the study by Azziz et al. (*ibid.*); 4) the authors suggest that although there are multiple benefits resulting from increasing insulin sensitivity in women with PCOS, including increased ovulatory frequency, decreasing circulating androgens, and improving hirsut-

ism, there might not be global improvement in all metabolic abnormalities associated with PCOS; 5) it is also possible that there are other lipids than the ones measured in the present study that are favorably altered in women with PCOS and result in beneficial effects on the cardiovascular system.

In any event, women with PCOS and increased insulin resistance appear to derive benefit from decreasing insulin resistance both with insulin-sensitizing agents (although not troglitazone) and weight reduction. It could also forestall the development of type 2 diabetes.—RBJ)

Ten Years' Experience With Alendronate for Osteoporosis in Postmenopausal Women

Henry G. Bone, David Hosking, Jean-Pierre Devogelaer, Joseph R. Tucci, Ronald D. Emkey, Richard P. Tonino, Jose Adolfo Rodriguez-Portales, Robert W. Downs, Jayanti Gupta, Arthur C. Santora, and Uri A. Liperman for the Alendronate Phase III Osteoporosis Treatment Study Group

Michigan Bone and Mineral Clinic, Detroit, Michigan; the Medical Research Center, Nottingham City Hospital, Nottingham, U.K.; Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; the Department of Medicine, Roger Williams General Hospital, Providence, Rhode Island; Radiant Research-Reading, Wyomissing, Pennsylvania; Good Health Associates in Adult Medicine, South Burlington, Vermont; Departamento de Endocrinología, Escuela de Medicina, Universidad Católica de Chile, Santiago; Virginia Commonwealth University, Richmond; Merck Research Laboratories, Rahway, New Jersey; and Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Petah-Tikva, Israel

N Engl J Med 2004;350:1189–1199

ABSTRACT

This multinational randomized double-blind trial, the Alendronate Phase III Osteoporosis Treatment Study, examined the results of alendronate therapy in postmenopausal women with osteoporosis who now have been followed for 10 years. A total of 227 women completed all phases of the study. Those participating were assigned to receive 5 or 10 mg of alendronate orally or placebo each day. The primary end point was the change in bone mineral density (BMD) in the lumbar spine. BMD also was measured at the femoral neck, trochanter, total proximal femur, forearm region, and the total body. From 17% to 31% of women in the various treatment groups had preexisting vertebral fractures. BMD continued to increase in the later years of the study in women given 5 or 10 mg of alendronate daily. The mean cumulative increase after 10 years in women taking 10 mg daily was 13.7%. Markers of bone remodeling (urinary N-telopeptides of type I collagen, bone-specific alkaline phosphatase) decreased, and this effect continued through 10 years of treatment. These markers increased within a year after alendronate was discontinued, although mean levels remained below baseline. There were no significant group differences in new vertebral fractures. The 3 groups also had similar safety profiles in the last 3 years of the study. No deaths were ascribed to alendronate therapy. Alendronate therapy continued to be effective over 10 years in these postmenopausal women, as estimated by both BMD measurements and effects on bone remodeling. The antifracture effect of alendronate did not appear to decrease over time.

EDITORIAL COMMENT

(Particularly after the premature termination of some of the effects of estrogen/progestin, and the Women's Health Initiative (WHI) study of more recently estrogen-only, treatment in post-

menopausal women reviewed elsewhere in this issue, which demonstrated reduction in fracture risk but resulted in a precipitous drop in estrogen/progestin use, the need for other methods of preventing and treating osteoporosis became even more important. Fortunately, alternative methods of treatment have become available. The most widely used of these include the bisphosphonates alendronate and risedronate, the selective estrogen receptor modulator (SERM) raloxifene, and more recently intermittent administration of a parathyroid hormone fragment (teraparotide), which actually restores bone. Most recently, as I reviewed in last month's issue of the *Survey*, Meunier et al. (N Engl J Med 2004;350:459) described the use of strontium ranelate in reducing the rate of vertebral fractures and also increasing bone density.

It is appropriate that adequate attention be paid to bone health and osteoporosis because it is a staggering medical and financial problem. In an excellent commentary on this present study of the 10-year results of treatment with alendronate, Gordon Strewler, a former faculty colleague at the University of California, San Francisco, points out that a 50-year-old woman in the United States has a 40% lifetime risk of an osteoporotic fracture and 1 in 3 women (and 1 in 9 men) over the age of 80 will sustain a hip fracture at some time, and 15% to 20% of these patients will die from attendant complications.

Strewler also indicates that, because of their unique pharmacokinetics, bisphosphonates such as alendronate are targeted directly to osteoclasts, the cells that resorb bone. Bisphosphonates bind to bone mineral when they are administered and then are slowly released as bone is resorbed by osteoclasts. Thus, oste-

oclasts are exposed to higher concentrations of bisphosphonates than are other cells.

It is hard to believe that alendronate, the first orally active bisphosphonate, was introduced into the United States 10 years ago. Alendronate increased bone mineral density, decreased bone turnover, and decreased the risk of vertebral and hip fractures in postmenopausal women with osteoporosis. Subsequent studies demonstrated that the benefits of treatment are maintained through 7 years of treatment.

In the present study by Bone [sic] et al., the results of 10 years of experience with alendronate are reported. The data demonstrate that the biochemical effects of alendronate on bone turnover remain stable over the span of 10 years of treatment without progression of its antiresorptive action or increase in the incidence of fractures. Because alendronate remains in bone for protracted periods, long-term data on safety and efficacy of bisphosphonates are important. In the present study, bone resorption was still inhibited by more than 50% 5 years after discontinuing treatment.

Thus, long-term safety and efficacy data are important. Whether other bisphosphonates behave in a similar fashion, including risedronate and the long-acting intravenously administered bisphosphonates approved for use in patients with cancer, but not yet in the general population, remains to be determined. It also would be useful to know how long alendronate and the others would exert beneficial effects after discontinuance. The data obtained to date appear promising, and further information will be informative and is necessary.—RBJ)

Effects of Conjugated Equine Estrogen in Postmenopausal Women Having Undergone Hysterectomy: The Women's Health Initiative Randomized, Controlled Trials

Women's Health Initiative Steering Committee

JAMA 2004;291:1701-1712

ABSTRACT

Although postmenopausal women have used estrogen for decades, its effect in preventing chronic diseases remains uncertain. This randomized, double-blind, placebo-controlled study chronicled the effects of estrogen alone in 10,739 postmenopausal women 50 to 79 years of age who had undergone hysterectomy. Participants received either 0.625 mg of conjugated equine estrogen (CEE) or a placebo each day. The primary outcome was coronary heart disease (CHD), including nonfatal myocardial infarction and death from CHD. The primary safety outcome was the incidence of invasive breast cancer. The study began in 1997 and was terminated early in 2004. Vital status is known for 95% of the randomized women. Follow up averaged 6.8 years. Compared with placebo recipients, the CEE-treated women had a greater reduction in low-density lipoprotein cholesterol (-13.7% vs. -1.0%) and a greater increase in high-density lipoprotein cholesterol (15.1% vs. 1.1%). Estimated hazard ratios (HRs) for CEE versus placebo were 0.91 for CHD, 1.39 for stroke, 1.34 for pulmonary embolism (PE), 1.08 for colorectal cancer, and 0.61 for hip fracture. The HR for breast cancer in the CEE group was 0.77. The global index of risks and benefits, including primary outcomes plus stroke, PE, colorectal cancer, hip fracture, and deaths from other causes, was 1.01. There was an absolute excess risk of 12 additional strokes per 10,000 person-years and a risk reduction of 6 fewer hip fractures. The estimated excess risk for all monitored events in the global index was 2 events per 10,000 person-years, not a significant effect. Women considering taking CEE should be told of the increased risk of stroke but could be reassured about the lack of any excess risk of CHD or breast cancer, at least for 6.8 years of use. CEE does not appear to confer overall benefit by preventing chronic disease in postmenopausal women. The findings support current U.S. Food and Drug Administration recommendations for postmenopausal women: to use CEE only for menopausal symptoms and to take the smallest effective dose for as short a time as possible.

EDITORIAL COMMENT

(This report of the estrogen-only arm of the Women's Health Initiative (WHI) and the decision to terminate this arm of the study prematurely received a great deal less media coverage and interest than the previously released report of the estrogen/progestin arm of the WHI, which also was terminated prematurely and caused a maelstrom of media, patient, and physician reaction. Among the possible reasons that the estrogen-only arm was not greeted with the same interest and alarm could be that 1) perhaps paradoxically, no increased risk of breast cancer was found in the estrogen-only arm of the study and hence could have been deemed less newsworthy; 2)

similarly, there was not an increase or decrease in coronary artery disease, in a way also less newsworthy than if a major difference one way or the other was found; and/or 3) the public has been so inundated with news about the WHI and HERS studies that they could be becoming immune to further information on this subject, and the news media could also have felt that it was no longer front page news. The significant negative finding in this study was a slight (8 per 10,000 women higher than in the placebo group) increased risk of stroke.

Nevertheless, despite the relatively small risk of harm, the study was terminated prematurely.

(I have heard that there was not unanimity for stopping the study among the WHI investigators and data monitoring committee, although I do not know this with certainty.)

So where does this leave us? Estrogen or estrogen/progestin should not be used primarily to prevent cardiovascular disease in either women who did or did not have a history of cardiovascular disease. However, this was never an approved indication for the medication by the U.S. Food and Drug Administration (FDA).

Why the differences between the results of this estrogen-only arm of the study and those of the earlier released estrogen/progestin arm? Again, at this point, we can only speculate. The most obvious difference is that in the estrogen-only arm of the study, women did not receive exogenous progestin. Readers may recall 2 earlier, smaller observational epidemiologic studies that I reviewed in the *Survey* in which taking estrogen alone was compared with estrogen plus progestin, and the incidence of breast cancer in the 2 groups was compared. (Schairer C, et al. JAMA 2000;283:485; Ross RK, et al. J Natl Cancer Inst 2000;92:328). In both of those studies, there was a higher incidence of breast cancer in the women taking both estrogen and progestin than those taking estrogen alone, particularly in the lean women, although the reason for this difference was not elucidated. When I asked one of our postdoctoral

fellows why this should be the case, she speculated that it could have reflected a higher circulating estrogen/progestin ratio in the women taking estrogen only, perhaps leading to increased breast stimulation. There are, of course, other explanations for this difference, and in general, women with increased weight tend to have higher increased extragonadal aromatization (the conversion of androgens to estrogen) in sites outside of the ovary, particularly in fat. Other possible explanations for the differences between the estrogen-only and estrogen/progestin arms in the WHI study are that the sample size of the estrogen-only arm was smaller, making it harder to demonstrate statistical differences; that the findings in one or the other arm was specious; or that unidentified confounding factors were not taken into consideration. It is easy to speculate when unencumbered by fact.

In any event, the study was stopped prematurely, and the advice from the FDA continues to be that estrogen and estrogen/progestin preparations should be used for symptoms, eg, relief for vasomotor symptoms (although they do also protect against excessive bone loss) for the shortest possible duration and the lowest effective dose. The greatest incidence of troublesome symptoms usually occurs in perimenopausal and early postmenopausal women, not the older patient population studied in the WHI.—RBJ)