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ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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Treatments for Leg Edema in Pregnancy

By Adriane Fugh-Berman, MD

ALTHOUGH PREGNANCY-ASSOCIATED LEG EDEMA IS NOT DANGEROUS, it can be very bothersome, causing pain, night cramps, and paraesthesias. Several factors associated with pregnancy may contribute to edema, including increased fluid volume and decreased smooth muscle tone in veins. Pressure of the gravid uterus may also increase venous pressure by decreasing venous return from the lower body. Treatments used for venous insufficiency in pregnancy are compression hosiery and leg elevation, but neither method has been adequately tested.

A Cochrane collaboration review identified only three randomized, controlled trials of treatments to reduce leg edema or to relieve symptoms.[1] One trial each of three treatments (rutosides,[2] external pneumatic compression,[3] and water immersion[4]) were included; a total of 115 women were subjects. The reviewers concluded that rutosides relieve symptoms of venous insufficiency in late pregnancy; that external pneumatic compression appears to temporarily reduce ankle swelling; and that immersion in water for 50 minutes results in diuresis and fall in blood pressure. It should be noted that these conclusions are based on only one trial of each treatment.

Rutosides

Rutosides are flavonoids derived from plants containing rutins (a rhamnoglucoside of quercitin, rutins are found in many plants, including tobacco, buckwheat, and eucalyptus). A placebo-controlled trial of 69 women in the Netherlands at 28 weeks gestation tested the effects of rutosides on improvement of symptoms.[2] Women were given placebo or rutoside capsules (300 mg tid) for eight weeks. Two-thirds of the 37 women given rutoside capsules noted an improvement in symptom scores (pain, feelings of heaviness and/or tiredness, nocturnal cramps, and paraesthesias), significantly higher than the placebo group, one-third of whom experienced improvement (odds ratio 0.30, 95% confidence interval 0.12 to 0.77). Changes in ankle circumference after eight weeks of treatment were also noted; there was a decrease in women receiving rutosides, while women given placebo had a small increase.

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Rutosides in a dose of 1000 mg/d have also been tested in healthy volunteers for induced leg edema. In a randomized, controlled, double-blind study with a placebo run-in, 12 volunteers stood motionless for an hour once a week, with before and after measurement of leg edema (by water displacement).[5] Compared to placebo, there was a progressive reduction in induced edema in the rutosides group, which was significant at the second and third weeks. Another study in healthy volunteers found that after three weeks of treatment with 1000 mg/d, halving the dose to 500 mg/d was adequate to maintain a beneficial effect.[6]

External Pneumatic Intermittent Compression

In a trial of 35 pregnant women in the third trimester with dependent leg edema, 17 women received external pneumatic intermittent compression (EPIC) for 30 minutes at 40 torr while in the left lateral position.[3] Eighteen women in the control group were placed in the same position but did not receive EPIC. Afterwards, both groups walked for 10 minutes. Four circumference measures were made before and after positioning and after walking. Compression had an immediate effect, but this effect had already lessened within 10 minutes. Later time points were not measured, and women were not asked whether symptoms were relieved, so it is unclear whether the effect of EPIC is clinically significant.

Immersion vs. Bed Rest

Shoulder-deep immersion in water resulted in greater diuresis and fall in blood pressure than either waist-deep immersion or 50 minutes bed rest.

A three-way crossover trial compared bed rest, waist-deep immersion in a bathtub, and shoulder-deep immersion in an immersion tank, with legs extended downward.[4] The water temperature in both immersion interventions was 32° C (90° F, about bathtub warmth). It is not stated how many women began the study but 11 women completed the study, which measured urine output and mean arterial pressure immediately after each 50-minute treatment period. There was no significant difference in urine output between bed rest and bathtub treatment. Diuresis after shoulder-deep immersion was significantly greater than the other two treatments. All treatments caused a significant decrease in mean arterial pressure; increased sodium and potassium clearance; decreased serum potassium levels; and decreased maternal heart rate. Neither immersion treatment produced a change in calculated plasma volume; the hour of bed rest produced a small but significant increase of 2.4% in plasma volume. Symptom relief was not recorded.

The authors of this study state that it demonstrates the safety of immersion, because significant diuresis without a change in calculated plasma volume indicates that fluid is being pulled from the extravascular space without decreasing intravascular volume. Although the immersion tank was specially constructed, the authors point out that shoulder-deep immersion can be done in a swimming pool. Aerobic exercise in water also increases diuresis.

Conclusion

Leg elevation and compression hosiery are the usual treatments for pregnancy-associated leg edema but shoulder-deep immersion appears to be a simple and effective treatment. (A Japanese bathtub is an option, although admittedly not the most accessible one. A hot tub with the temperature turned down may be another option.) Swimming and water aerobics may also be useful and are particularly comfortable exercises for pregnant women. Rutosides appear to be effective; although these plant-derived substances are unlikely to be toxic it bears noting that long-term toxicity studies have not been done in adults, nor has safety for fetuses been established. EPIC is cumbersome and appears to work only temporarily.

More research needs to be done in this area: simple, low-cost treatments for pregnancy-induced leg edema would be welcome. It would be useful to compare standard treatments with immersion and water aerobics, for

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example. Massage (especially lymphatic massage) also would be an interesting therapy to test for this problem. ❖

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Counseling Patients about Alternative Cancer Therapies

Part III of a Series

By Adriane Fugh-Berman, MD

PATIENTS WHO ASK ABOUT ALTERNATIVE CANCER THERapies clearly trust their doctors. However, physicians have difficulty providing counsel in this area, since they must walk the line between supporting their patients while endorsing only proven therapies.

There is a difference between using alternative therapies as adjuncts to conventional treatment and using alternative therapies as anticancer treatments (often instead of conventional treatment). In terms of adjunctive treatments, adequate evidence exists to support the use of certain alternative treatments, including hypnosis or acupressure bracelets for chemo-associated nausea and vomiting; massage for post-mastectomy lymphedema; and topical vitamin E for chemo-induced mucositis.

And it's common sense that cancer patients can benefit from a balanced diet, exercise, relaxation, social support, and stress reduction (whether by massage, meditation, yoga, or seeing more movies). In fact, everyone could benefit from these measures.

It is difficult to counsel patients about alternative cancer treatments because there is little evidence of benefit in this area. However, physicians should ensure that cancer patients know all their options by describing the known benefits or risks for specific cancer therapies (conventional or alternative); informing patients of the option to participate in clinical trials; avoiding recommendation of therapies (conventional or alternative) for which no clinical trial data exist; and remaining supportive of patients even when they make decisions against their physician's advice.

Resources

For conventional treatments, the National Cancer Institute (NCI) provides an invaluable resource called "CancerFax" that gives consumers and physicians frequently updated information about prognoses and treatments of choice for all kinds of cancer. To access this service, call (301) 402-5874 from any fax machine, and follow the commands to get a list of cancers and their codes. After identifying the appropriate code, call back and key in the code. Up-to-date information will be sent back to the caller's fax machine. Or visit NCI's website at http://www.nci.nih.gov.

NCI's telephone information service, (800) 4-CANCER, provides information in English and Spanish; people with TTY equipment should call (800) 332-8615.

For a current list of clinical trials, consult the PDQ database, which is accessible at medical and many other libraries, or at http://www.cancernet.nci.nih.gov/pdq.htm. This site also provides links to other clinical trials sites.

For patients whose cancers have high cure rates through conventional treatment, physicians have an ethical obligation to recommend against choosing alternative treatments (adjunctive treatments are fine). For example, early cervical cancer, endometrial cancer, and Hodgkin's lymphoma have very high cure rates when treated conventionally; it does not make sense for patients to eschew curative treatment when it does exist.

There is nothing to be gained by discouraging patients with poor prognoses or those who want to use alternative cancer treatments in conjunction with conventional treatments. Whether or not they agree with their patients' choices, physicians still play an important role in monitoring and supporting their patients. Descriptions of alternative cancer therapies can be found in several books; Michael Lerner's *Choices in Healing* is the best among them. It bears emphasizing that no large clinical trials have been completed on any alternative cancer therapies, and patients should be told that.

Many alternative cancer therapies are very expensive. Providers of alternative cancer treatments range from the sincere to the unscrupulous. Several services charge

patients hundreds of dollars for referrals to alternative practitioners; many of these referral services are staffed by people who are not health care professionals.

If patients are determined to try alternative cancer clinics, physicians can help them weed out the worst by providing the following list of questions to ask alternative cancer therapy providers:

Are all patients treated, or is there a selection process?
Be wary of clinics that accept all patients and/or claim that their therapy cures all cancers.

What's the success rate with my cancer?
High numbers or slick answers should arouse suspicion.

What does "success" mean?
Some clinics use their own unvalidated tests to mark cancer progression, prognosis, or the "success" of their therapy.

Can this therapy be used with conventional treatment or other alternative treatments?
It's a bad sign when someone states that their therapy must be used alone. There is a case to be made that the immunosuppressive effects of chemotherapy should not be combined with an immunostimulating therapy, but a blanket statement that surgery, radiation, or any other conventional therapy would "interfere" with a treatment should not be trusted unless backed by data. Patients should also ask about potential side effects.

Can I talk to some patients who have received this treatment (preferably patients who have had the same cancer as mine?)
This is a good question to test the level of suspicion or paranoia manifested by a clinic, and whether they actually can identify patients happy with their treatment. Some clinics that refuse may invoke patient confidentiality, but a responsible clinic should be able to contact a patient or two and ask whether they would be willing to be called by a potential patient. And obviously a place that gives out former patients' names and numbers without their permission does not care about patient confidentiality.

How much does it cost, and what does that fee include?
Some programs require extended stays, and lodging may add thousands of dollars to expenses.

Is the clinic staff willing to speak to my regular physician?
This is a good question to ask to help determine the clinic's level of paranoia. Willingness to talk to a patient's regular physician is a good sign.

Are records kept on how the treatment affects various patients?
Obviously, this is a minimal requirement.

Is there any long-term follow-up on patients?
A clinic that claims a high success rate but does not track patients after they leave the clinic is not trustworthy.

Recommendation

Regardless of whether patients decide to use conventional and/or alternative therapies, primary care practitioners should stay in regular contact with patients after a cancer diagnosis. Even when you are not making the decisions on chemotherapy regimens, you still can be a very important support to them during their health crisis. It may be a good idea to request that patients make regular appointments so they can discuss their experiences with a physician who knew them before their cancer diagnoses. Even when you "only" listen and provide comfort, your patients will appreciate your support immensely. ❖

Does Alternative Medicine Use in Breast Cancer Patients Connote Distress or Resilience?

Abstract & Commentary

Source: Burstein HJ, et al. Use of alternative medicine by women with early-stage breast cancer. *N Engl J Med* 1999;340:1733-1739.

Objective: To survey subjects on their use of conventional therapies, alternative medical treatments, and health-related quality of life during the first 12 months after diagnosis of early-stage breast cancer.

Subjects: Cohort of 480 women in Massachusetts with newly diagnosed, Stage I or II breast cancer who participated in a two-year statewide study of how women choose treatment for cancer. Of the 1,532 women potentially eligible to participate in the study, hospitals and physicians granted consent to contact 1,158, of whom 795 (69%) agreed to participate. Then hospitals were asked to approve an add-on study about subsequent medical care and health-related quality of life, including use of alternative medicine (AM).

Administrative delay and lack of hospital consent reduced the number of eligible women from 795 to 657. Of these, 536 completed a questionnaire at three months, and 480 completed a questionnaire at 12

months. All study analyses are limited to the 480 (73.1% of eligible participants) who completed the 12-month survey. Five of the 480 respondents reported a recurrence of breast cancer.

The 480 participants who completed the 12-month questionnaire did not differ from the 177 eligible women who did not complete the surveys by age, marital status, menopausal status, breast cancer stage, or type of surgery (mastectomy or lumpectomy). Respondents had significantly higher levels of education and income, were more likely to be white, and had fewer coexisting illnesses.

Methods: Patients who consented to participate received mailed questionnaires timed to arrive at three and 12 months after the initial surgery. Validated survey instruments were used to assess physical and emotional health and quality of life. "Summary scores" for physical and mental health were done at baseline, but at three and 12 months, repeat "summary scores" plus five other survey instruments were used.

Alternative medical therapies were divided into two categories: "healing therapies," which required physical action on or exposure of the body (diet, massage, megavitamins, chiropractic, homeopathy, acupuncture, herbal remedies, energy healing, and folk remedies), and "psychological therapies," which involved primarily mental processes (imagery, hypnosis, relaxation, biofeedback, spiritual methods, and self-help groups). The use of alternative therapies was classified as "none," "new" (initiated within one year after breast cancer surgery), or "continuous" (used both before and after surgery).

Results: The use of alternative therapies was common after breast cancer surgery, with 135 of 480 women (28.1%) using some type of AM for the first time. New AM use accounted for over 70% of all use. The 135 new AM users used an average of 2.5 different alternative treatments. Most patients (71%) reported that their physicians knew of their AM use. Women with Stage II disease and those who received chemotherapy were significantly more likely to initiate AM use, whereas women who were taking tamoxifen were significantly less likely to do so.

The study reports that all groups of patients had similar baseline mental and physical health scores. Although physical health scores were similar at the three-month survey, the mental health scores of new AM users had fallen from the baseline, whereas the scores for nonusers were higher than at baseline. On survey instruments initiated at three months, new AM users also reported more depression, less sexual satisfaction, greater fear of recurrence, and more numerous and severe somatic symptoms. At 12 months, all groups of patients had improved their mental and physical health scores, although new AM users still reported less sexual satisfaction and greater fear of cancer recurrence.

COMMENTS BY WILLIAM BENDA, MD AND CHARLEA T. MASSION, MD

Sometimes we find a study that is visionary in its implications but myopic in its conclusions. Burstein et al report that women with early-stage breast cancer who begin to use AM suffer more psychological distress, and therefore, new use of AM may identify the need for psychological, perhaps even psychiatric, intervention. However, another very plausible conclusion is that any woman faced with the loss of health and the specter of dying may experience extraordinary feelings of anxiety, depression, and vulnerability. The exploration of unconventional therapies and support from those practitioners may simply allow her to express emotions that are normal in the context of this intense health crisis.

In our time-stressed, managed care era, a patient is less likely to explore such territory with a physician than with a self-help group or a massage therapist. The "worsening" of mental health scores at three months may identify women who have the strength and willingness to confront their emotions and the implications of their disease early in the course of their treatment. It would be interesting to see the data beyond the 12-month completion of the study—perhaps those who chose alternative therapies eventually will suffer less psychological distress and experience better quality of life. This certainly was evident in Spiegel's studies on improved breast cancer survival in women who participated in support groups.[1] (Spiegel's well-known and respected research is curiously absent from this study's discussion and bibliography.)

The methodology must be called into question as well. There are several major problems with this study. First, although baseline summary scores for physical and mental health are reported, baseline scores are not provided for the five other survey instruments (the Medical Outcomes Study [MOS] sexual-satisfaction survey, the MOS 36-item short-form health survey, the Center for Epidemiologic Studies depression scale, the Lasry and Margolese scale for fear of breast cancer recurrence, and an expanded symptom checklist from the National Surgical Adjuvant Breast and Bowel Cancer Prevention Trial). Only three-month and 12-month scores are reported. Baseline differences in the scores of the two groups cannot be ascertained; the possibility exists that women who may have had lower baseline scores on these measures were more likely to have sought additional therapies, and

therefore cannot be fairly compared to those with higher baseline scores.

Second, the differences in scores were appropriately analyzed with the Wilcoxon rank-sum test, but the distributions of scores were displayed as means. This is inappropriate and prevents the reader from judging whether there were clinically important differences among women in the various groups. Just a few outliers can throw off the mean for the entire group.

Also, those who chose to participate in the survey were younger, more often white, had higher income and educational levels, and had fewer coexisting illnesses than the eligible non-participants. Based on previous research, white women with a higher socioeconomic status are more likely to seek alternative therapies anyway. This calls into question the authors' conclusion that women who are new AM users are more prone to psychological dysfunction. The truth may be that they are simply more likely to discuss their fears and feelings based on their prior experiences and behaviors. Thus, there may be an inadvertent, yet significant selection bias.

The above criticisms do not necessarily negate the validity of the overall study. However, to assume that seeking help which is generally unavailable in conventional medicine denotes psychological pathology rather than potential resilience reveals a disturbing biomedical bias, and offers troubling implications if the authors' "findings" change clinical practice without further research. In an accompanying editorial, Sloan Kettering's Dr. Jimmie Holland urges physicians to ask about alternative therapies to screen for women who need psychiatric consultation. In response, one breast cancer activist stated, "If physicians were to follow Dr. Holland's advice to consider new AM users for psychiatric referral, particularly in our age of managed care, women would be unlikely to encounter a sympathetic listener, but would probably be given a tranquilizer or antidepressant prescription, possibly soothing symptoms, but unlikely to deal with underlying fears or upsets."[2]

It's true that women with breast cancer are at higher risk for anxiety and depression and that their physicians need to be alert to these symptoms. It's also true that many physicians need to improve their screening for these conditions. One study of oncologists found that they markedly underestimated depressive symptoms in their most depressed cancer patients.[3] But why screen for depression by asking about AM use? DSM-IV describes a simple and inexpensive checklist for depression screening, or you may use the Beck, Zung, or other depression rating scales.

Perhaps further observation and evaluation of the new AM users could provide clues to help breast cancer patients become breast cancer survivors. Conceivably, AM use is a marker after all, but one of emotional health rather than psychopathology. In any case, the methodological problems with this study should be considered when judging its conclusions. ❖

Dr. Benda is a Senior Fellow in the Program in Integrative Medicine at the University of Arizona in Tucson, AZ; Dr. Massion is on the editorial advisory board.

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CME Questions

11. A study of immersion therapy for pregnancy-induced leg edema found that:
a. waist-high and shoulder-high immersion both increased diuresis.
b. only waist-high immersion increased diuresis.
c. only shoulder-high immersion increased diuresis.
d. neither intervention had an effect on diuresis.

12. Controlled trials have found that rutosides:
a. reduce pregnancy-related leg edema.
b. reduce induced edema in healthy volunteers.
c. reduce pain, cramps, and paraesthesias in pregnancy-related leg edema.
d. All of the above.
e. None of the above.

13. In a recent breast cancer study, women with Stage II disease and those who received chemotherapy were significantly more likely to initiate AM use than women who took tamoxifen.
a. True
b. False

14. Estriol is a weak estrogen used for HRT that:
a. decreases endometrial cancer risk.
b. increases endometrial cancer risk.
c. has no effect on endometrial cancer risk.

15. A recent crossover study of soy isoflavones in premenopausal women found:
a. increased luteal phase length.
b. increased follicular phase length.
c. no differences in length of luteal phase, follicular phase, or menstrual cycle.

With Comments from Adriane Fugh-Berman, MD

More Evidence that Estriol Isn't Safe

Source: Weiderpass E, et al. Low-potency oestrogen and risk of endometrial cancer: A case-control study. *Lancet* 1999;353:1824-1828.

Design and Setting: National population-based, case-control study in Sweden.

Subjects: 789 postmenopausal women with endometrial cancer and 3,368 controls (histopathological review reclassified 80 cancer cases as endometrial atypical hyperplasia).

Results: Five years oral use of estriol 1-2 mg/d increased the relative risk of endometrial cancer compared to never-use; the odds ratio was 3.0 for endometrial cancer and 8.3 for atypical endometrial hyperplasia. Ever-use of estriol was associated with a doubling of endometrial cancer risk compared to never-use. The association was stronger for well-differentiated cancers and excess risk was lost quickly on cessation of treatment. Only weak associations were noted for vaginal use of estriol and risk of endometrial neoplasia.

Funding: Research American Cancer Society grant EDT-89; NIH grant RO-1-CA 58427; grant from the Swedish Cancer Society.

Comments: Low-potency estrogen preparations, including estriol, are popular in Sweden (and are usually prescribed without a progestin). In North America, estriol has been promoted by alternative medicine practitioners as a "safe" estrogen that does not cause endometrial proliferation; claims have even been made that it reduces breast cancer risk. These claims were not based on reliable data. (See *Alternative Therapies in Women's Health*, June 1999, pp. 51-52.) Although estriol is weaker and shorter-acting than other estrogens used in hormone replacement therapy (HRT), assumptions of harmlessness were premature. This epidemiological study makes it clear that estriol has a significant adverse effect on endometrial neoplasia and should not be used without a progestin. ❖

Proteolytic Enzymes for Pancreatic Cancer

Source: Gonzalez NJ, Isaacs LL. Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. *Nutr Cancer* 1999;33:117-124.

Design and Setting: An open study in a private physician's office.

Subjects: Eleven patients (five women, six men) with biopsy-confirmed pancreatic cancer, who had not been treated with radiation or chemotherapy, Whipple procedures, or other major surgical treatment. Patients who had undergone exploratory surgery or simple biliary bypass were considered eligible.

At enrollment, eight patients had Stage IV disease (four of these had liver metastases) and three had inoperable Stage II disease. Seven had undergone biliary stent placement as a palliative treatment (only one of these underwent partial resection of the tumor). The remaining four patients underwent surgery during the study; three had biliary stents placed, and the fourth underwent total abdominal hysterectomy and oophorectomy for extensive metastatic disease.

Treatment: A three-part treatment involving diet, nutritional supplements, and coffee enemas. The diet excluded meat and poultry and emphasized raw, juiced, and lightly steamed vegetables. Eggs and yogurt were allowed daily, and fish three times weekly. Nutritional supplements included vitamins, minerals, freeze-dried organ concentrates including thymus and liver. Each patient took 25-40 g of a freeze-dried pancreas product in divided doses throughout the day. A patient typically took 130-160 capsules daily. As a "detoxification" treatment, coffee enemas were done twice daily.

Outcome Measures: Length of survival from diagnosis.

Results: One-year survival was 81% (nine patients); two-year survival was 45% (5 patients) and three-year survival was 36% (4 patients). At time of study publication, two patients were still alive.

Funding: Nestle Corporation.

Comments: This is a small but very interesting pilot study of an alternative cancer therapy that appears promising. It is commendable that this author tested the effects of his therapy on a poor prognosis cancer with limited treatment options.

The median survival of patients with unresectable pancreatic cancer is 17-22 weeks, while the median survival in this group was 17 months. According to Gonzalez, the pancreatic enzymes are the anticancer part of this treatment while the nutritional supplements are supportive and the coffee enemas combat side effects (including low-grade fevers, muscle aches and pains, and rashes).

This is exactly the sort of simple study with indisputable end points that should be encouraged. Gonzalez is one of the few ethical practitioners of alternative cancer treatments. He has been willing and motivated to assess his treatment by conventional medical standards (he has been working with the National Cancer

Institute for years on implementing a trial of his therapy, and a randomized, controlled clinical trial comparing the nutritional enzyme therapy with gemcitabine in patients with pancreatic cancer has been funded by the NCI). ❖

Soy and Hormone Levels

Source: Duncan AM, et al. Soy isoflavones exert modest hormonal effects in premenopausal women. *J Clin Endocrinol Metab* 1999;84:192-197.

Design and Setting: Randomized controlled crossover trial in Minnesota.

Subjects: Fourteen premenopausal women completed the study.

Treatment: High-isoflavone soy powder (2 mg/Kg/d or approximately 128 mg) compared with low-isoflavone (1 mg/Kg/d, or approximately 64 mg) and isoflavone-free (0.15 mg/Kg/d) soy powder.

Dose/Route/Duration: Subjects consumed three soy powders with varying isoflavone content during each of three periods lasting three menstrual cycles plus nine days. Washout period between each period was approximately three weeks. Otherwise, subjects consumed their regular diet with detailed dietary instructions on avoiding phytoestrogens, alcohol, and vitamin supplementation. Plasma estrogen, progesterone, LH, and FSH levels were collected every other day during the last six weeks of each diet cycle.

Outcome Measures: Plasma hormone concentrations, menstrual cycle length, and endometrial effects.

Results: The high-isoflavone diet decreased free T3 and dehydroepiandrosterone sulfate (DHEA-S) during the early follicular phase and decreased estrone levels during the mid-follicular phase. The low-isoflavone diet decreased LH and FSH during the periovulatory phase. There were no other significant changes in SHBG or hormone levels (including progesterone, testosterone, prolactin, androstenedione, throxine [T4], TSH, insulin, or cortisol) nor any change in the length of the menstrual cycle, follicular, or luteal phase. Three endometrial biopsies were performed on seven subjects during the study; another five women underwent two biopsies; none showed changes in histological dating.

Funding: NIH grant CA-66016 and general clinical research center grant MO1-RR-00400 from the National Center for Research Resources.

Comments: This is an excellent, well-thought out, carefully conducted trial that looked at multiple hormonal parameters. It is also the first crossover study to compare different isoflavone doses. It is very interesting that only small changes were seen in reproductive hormones (mainly mid-cycle surges of LH and FSH). Although several previous studies found different results on reproductive hormones and menstrual cycle length (see *Alternative Therapies in Women's Health*, January 1999, pp. 12-14), this study was longer than previous studies and examined more parameters more carefully. It is the definitive study on this subject so far.

I have only two criticisms. The first is that baseline levels of hormones were either not drawn or not reported. In other words, all diets in this study contained soy, although subjects consumed isoflavone-free soy during some cycles. The reason that this is important is that it is possible (although admittedly not probable) that other substances in soy besides isoflavones affect hormone levels. The second criticism is that washout periods could have been longer. One uncontrolled high-dose isoflavone (200 mg/d) study in six premenopausal women that did find an effect of soy on hormone levels found that the effect lasted for two to three cycles.[1]

There has been some concern that soy may have an adverse effect on thyroid function because in vitro studies show an inhibition of thyroid peroxidase. In this study, although free T3 levels were significantly lower in the high (but not the low) isoflavone group, there were no changes in free or total T4, total T3, or TSH levels. Some animal studies have found that soy intake increases T4,[2] so it is possible that soy isoflavones inhibit conversion of T4 to T3. Although this has no immediately apparent clinical relevance, it is theoretically possible over time that metabolic rate could decrease. In this study, no changes were seen in body weight, body mass index, or percent body fat. A study of long-term effects of high-isoflavone supplementation on thyroid function tests and metabolic rate would be interesting. ❖

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