## Analyzing the HABITS data: Is HT safe in women with previous breast cancer?

Holmberg L, Anderson H, for the HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped [research letter]. *Lancet*. 2004;363.

**OBJECTIVE** To evaluate the safety of hormone therapy (HT) compared to nonhormone therapy (NHT) in women with previously diagnosed breast cancer who are experiencing menopausal symptoms.

**RESULTS** Researchers found an increased risk of breast cancer recurrence among women taking HT, with 14% developing recurrence/contralateral breast cancer compared with 4% of nonusers, and terminated the trial early.

**METHODS** Women were eligible for the HABITS prospective randomized trial if they had a history of in situ, stage I or II breast cancer with up to 4 positive lymph nodes and climacteric symptoms. Both premenopausal and postmenopausal women were accepted into the study, which began accruing participants in May 1997. The trial assigned 434 previous breast cancer patients with menopausal symptoms to either HT or NHT.

The main endpoint was any new breast cancer event (recurrence/contralateral breast cancer), with all analyses done according to intention to treat. Secondary aims were to examine quality of life and risk of death from breast cancer.

After a median follow-up of 2.1 years, 26 women in the HT group and 7 nonusers had a new breast cancer event. All women in the HT group and 2 women in the NHT group were exposed to HT; most experienced their event while on treatment.

**OUTCOME** Researchers determined that HT posed an unacceptable risk and ended the trial on Dec 17, 2003.

**EXPERT COMMENTARY**

**Imperfect study design.** Although it was a prospective randomized trial, HABITS leaves much to be desired. It was an open study that was neither placebo-controlled nor blinded.

Treatment was not described in either arm of the study. For example, HT was suggested to be estrogen with or without progestin of "median potency" (undefined), similar to that "commonly given in the environment where the patient lives and the clinician works." In the NHT arm, therapy was the "best symptomatic treatment without hormones" and could include clonidine, beta blockers, psychological support, physical exercise, and acupuncture. Local estrogen could be used but "natural products" could not. In 2002, because of poor accrual, the "Stockholm" study was folded into the HABITS trial.

The HABITS study was an equivalency trial designed to stop if the hazard ratio (HR) surpassed 1.36. The investigators state that the HR for HT was 3.5 (14% of women had a recurrence/contralateral cancer, compared with 4% in the nonhormonal group). The investigators note that the Stockholm trial had an HR of 0.82 and was not included in the research letter published in *Lancet*. Since most HABITS participants were from Sweden, one wonders why there are such different results from the same apparent population base.

**Unanswered questions.** Analyzing the

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HABITS trial is problematic on several fronts. For instance, mammograms and follow-up are suggested but apparently not required (more than 20% of randomized women were not included in the analysis because they had not had at least 1 follow-up visit). Were these items equal in both groups? Did the HT group have better mammography compliance than the nonhormonal group? Compliance to therapy was not detailed.

Roughly 20% of women in the HT group who developed a recurrence were not on HT at the time of recurrence. With such a short follow-up (2.1 years), details on the length of HT and relationship to time of randomization and recurrence are important. Since breast cancer can reside in the breast for 10 years or more before diagnosis, it is reasonable to assume that the recurrences and contralateral breast cancers were present at the time of randomization.

Two of the most important risk factors in breast cancer are stage and lymph-node status. These 2 items were not stratified at the time of randomization. Were they equal in the 2 groups? What was the receptor status in each group? Were the groups equal in this regard?

Tamoxifen was allowed and stratified at randomization. Since tamoxifen can have an impact on menopausal symptoms, was compliance the same in the 2 groups?

Although the authors noted that a Cox proportional hazard model would be used in their analysis, no such data was given. The results could change once such a model is used.

**BOTTOM LINE** We appreciate that a study like this is difficult, as the Women's Health Initiative amply proves. This one involved low accrual and lenient guidelines regarding treatment, prognostic variables, and compliance. Still, this preliminary research letter is just that: preliminary. We should await thorough evaluation before giving the findings much credence. Certainly the statement in the commentary accompanying this letter, that this study "can now reasonably guide clinical practice for women with breast cancer," appears premature and without merit.

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## Does antibiotic prophylaxis with extended coverage limit postcesarean infection?

Andrews WW, Hauth JC, Cliver SP, Savage K, Goldenberg RL. Randomized clinical trial of extended spectrum antibiotic prophylaxis with coverage for *Ureaplasma urealyticum* to reduce post-cesarean delivery endometritis. *Obstet Gynecol*. 2003;101:1183-1189.

**OBJECTIVE** To determine whether extended-spectrum antibiotic prophylaxis that targets *Ureaplasma urealyticum* reduces postcesarean endometritis.

**RESULTS** Following cesarean, the frequency of endometritis, wound infections, and a combination of the 2 was significantly lower among treated women than women given placebo.

**METHODS** The 597 women enrolled in this randomized, double-blind trial all were given cefotetan prophylaxis after cord clamping at cesarean delivery. Subjects then were randomized to receive doxycycline plus azithromycin (n = 301) or placebo (n = 296). Both groups were monitored for endometritis, defined as a

fever of 100.4° F or higher with 1 or more supporting clinical signs (maternal tachycardia, foul-smelling or purulent lochia, tender uterus, and maternal leukocytosis) or as a physician diagnosis of endometritis and no nonpelvic source of fever. Among study participants, 56% were black, with an age of 25.5 ± 6.2 years, and 43% were nulliparous. Groups were similar for race, parity, maternal age, and most risk factors for postcesarean endometritis.

**OUTCOME** Postcesarean endometritis occurred in 16.9% of treated women versus 24.7% of controls ($P = .02$), and wound infections affected 0.8% of treated women versus 3.6% of controls ($P = .03$).

Although the 2 groups were dissimilar for maternal leukocytosis (24.9% of treated women versus 12.5% of controls, $P = .042$) and classic uterine incision (7.6% versus 12.5%, $P = .048$), adjusting for these factors did not alter the risk ratio for postcesarean endometritis in the active versus placebo-treated groups (relative risk 0.65, 95% confidence interval 0.43-0.98).

Length of stay was longer in the placebo group (104 ± 56 versus 95 ± 32 hours, $P = .016$) and among women with endometritis (146 ± 52 versus 127 ± 46 hours, $P = .047$).

**EXPERT COMMENTARY** This study tried to demonstrate that *U. urealyticum* is a significant pathogen and the etiologic agent for postpartum endometritis. However, the fact that *U. urealyticum* is found in the genital tract of approximately 70% to 90% of women does not support the thesis that it plays a major role in the microbial pathogenesis of postpartum endometritis.

Just because a microorganism is present in the lower genital tract does not mean that, in a state of infection, it is the etiologic agent. For example, many women harbor *Enterococcus feacalis* or *Staphylococcus epidermidis* in the genital tract; these often are isolated along with other bacteria from the site of infection. Yet the infection often is treated with antibiotics that offer no activity against these bacteria.

**Lack of bacteriology limits relevance.** Upon first analysis, this study appears to be sound, since it is both randomized and blinded. However, a major flaw weakens the conclusions significantly: lack of bacteriology.

The researchers neglected to obtain specimens for culture of bacteria from the uterus of each infected patient. Instead, they relied on statistical analysis, comparing the endpoint of infection versus no infection to extrapolate as to the cause. They failed to realize that the antibiotics used for prophylaxis—specifically doxycycline and azithromycin—also provide activity against Gram-positive and Gram-negative bacteria that make up the endogenous bacteriology of the vagina.

If endometrial specimens had been obtained from each infected patient, they would have provided a database on the frequency of involvement of the bacteria causing endometritis.

The authors do not state why they chose to use both doxycycline and azithromycin. In regard to the activity of these antibiotics against *U. urealyticum* there is probably not much difference as to efficacy.

**BOTTOM LINE** The use of combinations of antibiotics for surgical prophylaxis is not advisable because it can lead to the selection of resistant strains that will remain in the patient's lower genital tract. Therefore, I would not use a cephalosporin plus doxycycline and/or azithromycin as a regimen for surgical prophylaxis. Before such a combination can be recommended, further study is necessary that includes microbiology to establish which bacteria are responsible for postpartum endometritis. The microbiological studies must be quantitative—not qualitative—before conclusions can be drawn and clinical recommendations made. ■

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