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INSIDE

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The Effect of Maternal Alcohol Consumption on Fetal Growth and Preterm Birth

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Low levels of alcohol consumption during pregnancy is not associated with SGA or preterm birth. Conversely, higher levels of alcohol intake during pregnancy are associated with an increased risk of preterm birth, even after ceasing alcohol intake before the second trimester.*

Source: O'Leary CM, et al. The effect of maternal alcohol consumption on fetal growth and preterm birth. *BJOG* 2009;116:390-400.

IT HAS BEEN VERY DIFFICULT TO STUDY THE EFFECTS OF ALCOHOL ON the fetus and on pregnancy, in general, because one depends so heavily on a patient's candor regarding true alcohol consumption and the effect of confounding variables, such as smoking. In Australia, drinking some alcoholic beverages in pregnancy is quite common, and, as opposed to the United States where drinking even the smallest amount of alcohol is strongly discouraged, the Australian National Health and Medical Research Council in 2001 recommended that "if women choose to drink during pregnancy, they should have less than 7 standard drinks per week and, on any one day, no more than two standard drinks."[1]

With this backdrop in mind, a group of Australian investigators studied a random sample of 4719 women who delivered in Western Australia between 1995 and 1997. The sample represented 10% of births in the region, and information regarding alcohol consumption was obtained via questionnaires sent out after birth. The authors were interested in 2 outcomes: the number of preterm births — defined as those delivering before 37 weeks — and the incidence of small-for-gestational age (SGA) births. To quantify the latter

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outcome, an optimal birth weight was calculated using the sex of the infant, maternal height, parity, and gestational age. Then the actual birth weight was matched up to this and, if it was below the 10th percentile, the infant was considered to be SGA.

As to alcohol consumption, the authors coded "low" as < 3 drinks per week, "moderate" as 2-5 drinks per week, "heavy" as > 7 drinks per week, and "binging" as > 2 drinks at a time (although this was difficult to sort out from the paper). In this random sampling, about 50% did consume some alcohol during pregnancy. Those in the low-level category who continued to drink showed little change in their drinking patterns. However, in all the other categories, there was a general decrease in the average consumption of alcohol. Interestingly, the percentage of heavy and binge drinkers decreased by two-thirds during pregnancy.

The punch line is that in each category there was no statistically significant difference in the rate of preterm birth in any category compared with abstainers. However, if data from the low-level group, representing the largest study group, were excluded from the analysis, then there was a 78% increase in preterm births over abstainers. The incidence of SGA was higher among heavy and binge drinkers (13%), compared with the rate in the overall population (8.9%). However, since the heavy and binge group was heavily spiked with smokers, there was no difference in the incidence of SGA when the authors accounted for this confounding variable. The strangest result was that heavy drinkers who stopped drinking before the second trimester had the highest rate of preterm birth.

■ COMMENTARY

In a matter of 40 years, the pendulum has swung from clinicians infusing huge amounts of IV alcohol to stop preterm labor to, now, telling patients that any amount of alcohol consumed by a mother may be dangerous to the health of her fetus. In Europe and, now I realize, in Australia, there is a more relaxed approach to alcohol and pregnancy. The above study does not address the effects of alcohol in small doses on the fetal brain, but it does address two issues — its effect on fetal growth and preterm birth. The bottom line is that, with one exception, there is no major effect on these two outcomes, if the confounding variable of maternal smoking is taken into account.

The surprise finding was that when heavy or binge drinkers stopped drinking after the first trimester, they had the highest rate of preterm birth (13%). The authors postulate that sudden abstinence "may trigger an inflammatory or other metabolic response resulting in an elevation of cytokines" responsible for preterm labor. My guess is that this result could have been due to the small numbers of patients in this category (type 1 error). However, the authors justifiably make the case that if heavy or binge drinkers were to stop or modify this activity before or in early pregnancy, we would not have to worry about this unexpected finding.

Speaking of worry, a few years back we were interested in correlating measurements of certain areas of the fetal brain with alcohol consumption and, then, later, with sophisticated testing of reaction times in the same children. To make a long story short, we found that indirect measurements of the size of the fetal frontal lobe correlated inversely with the amount of alcohol consumed. This, in turn, correlated with how poorly the children performed during the above testing process. However, there was no discernible effect unless the average alcohol consumption exceeded 2.9 drinks per day at the time of entry into the study.[2,3]

Smoking and alcohol certainly seem to go together, even in pregnant women. For example, the two of us doing the fetal ultrasound measurements in the above study were supposedly blind to which patients were imbibers and which ones were controls, but it became immediately clear who was who, because, often, soon after the "exposed" patients walked in, the ultrasound room smelled like the smoking lounge at Denver International Airport.

At least one-third of those in the "exposed" group in our study were in the restaurant business where it is common to have "a pop or two" before going home, and

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most of these individuals stopped after finding out (sometimes late) that they were pregnant. Many of them seemed to exude guilt, fueled by all the warnings out there against any exposure to alcohol. Fortunately, most available data suggest that their guilt is likely unfounded, since it appears at this time that to create full-blown fetal alcohol syndrome, or, it seems, to cause even less severe effects on the fetal brain, larger amounts of alcohol would need to be consumed regularly. The Australian study indicates that the same could be said for preterm birth and IUGR. Although smaller amounts of consumed alcohol cannot be completely excluded as having subtle effects on the fetal brain, there is much more evidence out there to indicate that smoking is more detrimental to the fetus than an occasional glass of wine. ■

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Long-acting Contraception for Pain Control in Patients with Endometriosis

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman is a consultant for Schering-Plough (as an Implanon trainer); she has received no funds from Schering-Plough in the past 12 months.

Synopsis: *After 6 months of use, both depot medroxyprogesterone acetate and the contraceptive implant (Implanon®) significantly decreased pain associated with endometriosis.*

Source: Walch K, et al. Implanon versus medroxyprogesterone acetate: Effects on pain scores in patients with symptomatic endometriosis — a pilot study. *Contraception* 2009; 79:29-34.

FORTY-ONE WOMEN WITH SYMPTOMATIC, HISTOLOGICALLY proven endometriosis (Stages 1-4) were randomized to receive either a contraceptive implant (Implanon®) or depot medroxyprogesterone acetate (DMPA). Women were followed every 3 months to report their dyspareunia, dysmenorrhea, and non-menstrual pelvic pain on a 100 mm visual analog scale (VAS; 0 = no pain, 100 mm = maximum pain). In addition, bleeding patterns and satisfaction were monitored. Prior to treatment, women reported an average pain score of 65 mm and after 6 months, a pain score of 30 mm or, in other words, a mean decrease in pain scores of 68% (95% confidence interval [CI], 53-83) with the implant and 53% (95% CI, 28-79) with DMPA (P = 0.36). In addition, significant improvements in pain scores were seen as early as 3 months of use. Overall, bleeding patterns were similar between the two groups. Equivalent rates of women reported being satisfied or very satisfied with either treatment (implant 57%, DMPA 58%), but a higher proportion of women reported being dissatisfied or very dissatisfied with DMPA (implant 9%, DMPA 32%).

■ COMMENTARY

Improvement in pain via surgical and/or medical management is often the main goal of endometriosis treatment. Many contraceptives have additional health benefits beyond their primary purpose of pregnancy prevention. Oral contraceptives, DMPA, and the levonorgestrel-secreting intrauterine device have all been shown to improve pain associated with endometriosis.[1-3] Walch and colleagues designed their study to determine if the progestin-only implant provided similar relief to DMPA for women experiencing pain due to endometriosis. Although this study was performed in a small group of women, Walch et al provide compelling evidence for the progestin-only implant as another effective treatment option for pain associated with endometriosis. In addition, unlike surgical treatment, medical treatment with hormonal suppression appears to provide greater long-term pain relief. This particular study demonstrated that pain scores were persistently lower among both DMPA and implant users at 12 months of use.

The contraceptive implant (Implanon) is known for its unpredictable bleeding patterns,[4] but the patterns reported in this study were similar between the two treatment groups. The majority of women in both groups reported "prolonged" (more than 14 days of continuous spotting or bleeding in 90 days) and/or "frequent" (more than 5 episodes of spotting or bleeding in 90 days) bleeding. The similarity in bleeding profiles during the study may be due to tracking DMPA's bleeding patterns through its typical 6-9 month "transition" period where we expect

more women to have unpredictable bleeding with DMPA use. The authors do report an improvement in bleeding pattern with greater duration of use but do not provide more specific data. We can probably get a better sense of how women reacted to bleeding patterns by looking at participants' satisfaction and reasons for study withdrawal. More women in the implant group were "dissatisfied" with the bleeding pattern but only 2 women withdrew from the study because of bleeding. Overall, more women in the DMPA group reported being dissatisfied with the treatment but not because of the bleeding pattern (i.e., weight gain, mood disorders, etc.).

Both the contraceptive implant and DMPA appear to be reasonable treatment options for pelvic pain due to endometriosis. Extrapolating the findings of this study, women can expect to have their pain decrease by 50% at 6 months of use, but improvements in pain can be seen almost immediately with initiating either treatment. However, improvement in pain may be offset by some minor side effects, which may or may not be tolerable depending on the patient. ■

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Lymphadenectomy in Early-stage Endometrial Cancer?

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is a retained consultant for GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer; and serves on the speakers bureau for OrthoBiotech.

Synopsis: *The intrinsic therapeutic value of lymphadenectomy for endometrial cancer has been debated since pathological-based staging was introduced in 1988. The ASTEC trial is the second and largest phase III study to address this hypothesis and, while acknowledging the procedure is the most precise to determine disease extent, the results suggests the procedure is of little or no benefit in and of itself.*

Source: Kitchner H, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): A randomised study. *Lancet* 2009;373:125-136.

THE STANDARD PRIMARY SURGICAL INTERVENTION FOR early-stage uterine cancer is hysterectomy, usually with removal of the adnexa. The role of other tissue evaluation, such as cytology and lymphatic survey, is to identify the presence of extrauterine disease. Heretofore, the therapeutic impact of routine lymphadenectomy on overall survival in this disease has been the subject of non-randomized prospective and retrospective comparisons. The ASTEC (A Surgical Trial in Endometrial Cancer) trial was conducted to address this hypothesis in a phase III randomized setting. In this multi-institutional trial, 1408 women with histologically proven endometrial cancer considered preoperatively to be confined to the uterine corpus were randomly allocated to either hysterectomy and bilateral salpingo-oophorectomy (BSO) or the same procedure with pelvic lymphadenectomy. Peritoneal cytology and palpation of the paraortic lymphatics were allowed in both groups. Risk strata were assigned postoperatively based on uterine findings (independent of node status). Those with intermediate risk for extrauterine disease were secondarily randomized to adjuvant pelvic radiotherapy or observation. Vaginal brachytherapy was administered at the discretion of the treating physician, as was the therapy for low-risk and high-risk disease. These latter two groups were not controlled for type of adjuvant therapy.

The primary objective of the study was overall survival (OS) and was powered to detect a 10% increase in the 5-year survival rate (from 80% to 90%). In the intent-to-treat analysis for OS, the hazard ratio (HR) was 1.16 (confidence interval, 0.86-1.54; $P = 0.31$); a similar finding was observed for the adjusted relapse-free survival (RFS; HR, 1.04; CI, 0.74-1.45; $P = 0.83$), although, there was superiority in RFS for standard surgery before making the adjustments for baseline characteristics and pathology details. Surgical complications were uncommon in both groups, but more frequently observed in those with more extended surgery. The investigators concluded that the procedure of lymphadenectomy did

not improve OS or RFS in women undergoing hysterectomy for suspected early-stage endometrial cancer and, as such, they could not recommend the procedure as routine practice outside clinical trials.

■ COMMENTARY

The long-awaited final results of this important clinical trial are no doubt going to be met with strong criticism and commentary as they are carefully dissected over the next several months. In 1988, the staging algorithm for endometrial cancer was adjusted to consider surgical-pathological findings at extirpation, which included lymphadenectomy. The primary reason for this alteration came in response to a number of large clinicopathological observational studies that demonstrated a relationship between depth of myometrial invasion and grade to the probability of extrauterine (predominately lymphatic) disease.[1] Early on, strategies to intraoperatively determine in whom lymphatic dissection should be performed were championed, but were generally found to be of poor reproducibility. This led to the "staging for all" position and was supported by non-randomized data suggesting a therapeutic advantage for systematic lymphadenectomy.[2] For the most part, the change in staging paradigm proved to be prognostic as well as informative, and clinicians found that the added information of extrauterine disease of merit in determining postoperative therapy. However, the direct impact of lymphadenectomy had not been subject to rigorous investigative hypothesis testing. The ASTEC trial suggests the procedure itself may not be associated with direct therapeutic benefit. Unfortunately, this is only part of the story, as the trial did not address the utility of lymphadenectomy to identify those patients in whom specific therapy should be administered, it did not control for adjuvant care in either low-risk or high-risk cases, and it considered only pelvic nodes dissection. An imbalance of patients in the lymphadenectomy trial was noted with higher rates of stage IC and non-endometrioid histology, which could have imbalanced the risk for death between the arms despite the randomizations. In addition, the allowance of "inspection" of the paraortics did lead to a number of patients in the control cohort being identified with "high-risk" disease.

Despite the obvious variances, the trial is supported by a second and independently conducted randomized phase III trial recently reported (CONSORT trial), which demonstrated the same effect on OS and RFS.[3] In contrast to ASTEC, this randomized trial of 514 patients did not control for postoperative adjuvant therapy. While findings from these trials may be at odds with our underlying bias, the real pitfall may be more realistically attributed to the disease population studied. In both trials, and as often observed in adjuvant therapy studies, the expected survival is quite high and very difficult to improve upon. In addition, nearly a third of patients succumb to non-disease-related events, such as heart disease. Careful construction of a study with appropriate controls for risk strata and adjuvant therapy will need to be performed to address the hypothesis of therapeutic lymphadenectomy in early-stage uterine cancer. ■

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Special Feature

The LIBERATE Tibolone Trial in Breast Cancer Survivors

By Leon Speroff, MD, Editor

THE LIVIAL INTERVENTION FOLLOWING BREAST CANcer: Efficacy, Recurrence, And Tolerability Endpoints (LIBERATE) trial was a multinational, placebo-controlled, randomized study of women with vasomotor symptoms who had had breast cancer surgically treated within the previous 5 years.[1] The study was designed to demonstrate that tibolone was superior to placebo, but when the DMSB notified the sponsor (Schering-Plough, formerly Organon) that there appeared to be an excess of breast cancers in the treated group, the sponsor canceled the trial on July 31, 2007, 5 months before its scheduled end.

The median duration of participation and treatment was about 3 years, with a wide range from a few weeks to almost 5 years. The participants used a variety of adjuvant treatments, including tamoxifen (66.8%) and aromatase inhibitors (6.5%). The dose of tibolone was 2.5 mg daily. Final numbers for analysis were 1556 women in the treated group and 1542 in the placebo group. The women ranged in age from younger than 40 to 79 years,

with a mean age of 52.7 years.

Positive lymph nodes were reported in 57.8%, and 70% had a tumor stage of IIA or higher. Estrogen receptor status was known in 2808 women in whom the tumors were estrogen receptor-positive in 77.8%. In the intent-to-treat analysis, the hazard ratio (HR) for recurrent breast cancer in the tibolone-treated women was 1.40 (confidence interval [CI], 1.14-1.70). The absolute risk for tibolone was 51 cancers per 1000 women per year, and 36 in the placebo group. The increase occurred only in women with estrogen receptor-positive tumors. There was no difference in mortality rates between the 2 groups during the 5-year study period. There were no differences in cardiovascular events or gynecologic cancers, and, not surprisingly, vasomotor symptoms, quality of life measures, and bone density improved with tibolone treatment.

The argument that postmenopausal hormone therapy should not be given to women who have had breast cancer is reasonable. It is based on the recognition of a large body of evidence that indicates that breast cancer is a hormone-responsive tumor. The overriding fear of many clinicians and patients is that metastatic cells are present (perhaps being controlled by various host defense factors) that may be susceptible to stimulation by exogenous hormones. However, many women who have had breast cancer are aware of the benefits of postmenopausal hormone treatment and are asking clinicians to help make this risk-benefit decision. In addition, some women suffer from such severe hot flushes and vaginal dryness that they are willing to consider hormonal treatment.

Tibolone Chemistry

Because of its unique metabolism, tibolone can exert different hormonal activities at different sites. This unique characteristic is precisely what makes the drug difficult to understand. Tibolone is structurally related to the 19-nortestosterone progestins used clinically in oral contraceptives; however, its activity depends on its metabolism. Tibolone is metabolized by human and nonhuman primates into 3 biologically active metabolites: The 3α-hydroxy (3α-OH) metabolite and the 3β-hydroxy (3β-OH) metabolite have estrogen-agonist properties, whereas the Δ-4 ketoisomer has progestogenic and androgenic effects (the Δ-4 isomer is produced in endometrium, accounting for tibolone's protection against endometrial proliferation). Although tibolone itself binds to the estrogen receptor, in vivo the activity of the 3-hydroxy metabolites is 100 times greater, with a greater affinity for the α-estrogen receptor than for the β-estrogen receptor. The metabolism of the parent compound is rapid and very near total, yielding mainly the 3α-OH and the 3β-OH metabolites in the circulation; the level of the 3α-OH metabolite is three-fold higher compared with the 3β-OH metabolite. Tibolone and the Δ-4 isomer can be detected only at peak levels 2 hours after ingestion, and even then, the levels are very low, at the limit of detection.

Previous Studies with Tibolone

How do the LIBERATE results that indicate an estrogenic action of tibolone in breast cancer survivors jibe with the literature indicating that tibolone exerts a nonestrogenic effect on breast tissue? Indeed, it was realistic to expect tibolone to have a salutary effect on the breast. It is well documented that the breast responds to tibolone with less stimulation compared with estrogen, judged by changes in mammographic breast density and the characteristics of tissue obtained by fine-needle aspiration. In the LIFT clinical trial that had vertebral fractures as the primary endpoint and breast cancer as a secondary endpoint, the risk of breast cancer after 3 years was significantly 68% reduced with tibolone treatment, although the dose was lower, 1.25 mg daily (HR, 0.32; CI, 0.13-0.80).[2]

The breast is a complicated estrogen factory. Breast tissue, normal and abnormal, contains all the enzymes necessary for the formation of estrogens (sulfatase, aromatase, and 17β-hydroxysteroid dehydrogenase) and the conversion of estrogens into their sulfates (sulfotransferase). The major pathway of estrogen synthesis in human breast tumor cells is by conversion of estrone sulfate to estrone by estrone sulfatase, a pathway that is more important than the aromatase pathway. Estrogen concentrations in the breast are higher in women with breast cancer, and formation of estradiol from sulfated estrogen is the primary pathway. Most importantly, this increase in estrogen activity is independent of the estrogen-receptor status of the tissue.

Tibolone and its metabolites inhibit estrone sulfatase and 17β-hydroxysteroid dehydrogenase in normal stromal cells and in hormone-dependent breast cancer cells (MCF-7 and T-47D). This inhibits conversion of estrone sulfate to estradiol. In addition, tibolone and its 3-hydroxy metabolites increase the conversion of estrone back to estrone sulfate by increasing the activity of sulfotransferase. Tibolone and all 3 metabolites inhibit the conversion of estrone to estradiol by 17β-hydroxysteroid dehydrogenase. Although these effects resemble progestin activity, tibolone is more potent. These biochemical effects in response to tibolone should lower estrogenic stimulation of the breast, and at least with normal breast cells in vitro, tibolone increases cellular differentiation and stimulates apoptosis. Thus, in cell line studies, tibolone acts like progestins and weak androgens as

measured by proliferation, differentiation, and apoptosis.

Postmenopausal hormone therapy increases breast density on mammography in about 10-20% of estrogen users and about 20-35% of estrogen-progestin users, an effect that occurs within the first months of treatment. In contrast, tibolone does not increase breast density, and causes far less mastalgia than that seen with estrogen treatment. It is logical to conclude that these favorable responses are a consequence of the tibolone effects on the breast tissue enzymes involved in local estrogen production.

The authors of the LIBERATE report point out that the previous literature documenting beneficial actions of tibolone on the breast reflect the impact of tibolone on normal breast tissue, and tibolone's activity to lower local bioactive estrogen levels in target tissues might be lost in cancer cells. The contrary results in the LIFT trial could reflect its older population of women at high risk for fractures, a population that also differed by having lower body weights, no history of tamoxifen treatment, and lower risk factors for breast cancer.

Studies with Estrogen or Estrogen-Progestin

The rate of recurrent breast cancer in hormone users has been reported in case series totalling more than 1000 breast cancer survivors. It is reassuring that the recurrence rates in these reports are not different from the expected rate of breast cancer recurrence. These patients have had both positive and negative nodes and positive and negative estrogen-receptor status. Although the results conform to an incidence of recurrent disease no greater than expected, the outcomes can reflect biases in clinician and patient decision-making that can only be overcome with a proper long-term, randomized clinical trial. A case-control study of hormone therapy after breast cancer actually found a significant reduction in risk of recurrent disease, breast cancer mortality, and total mortality in hormone users.[3] Again, although these are reassuring data that hormone therapy after breast cancer has no adverse impact on recurrence, they are observational in origin.

HABITS (Hormonal Replacement After Breast Cancer—Is It Safe) was initiated in May 1997, recruiting patients from multiple centers in Sweden. A similar trial was initiated in Stockholm. Because recruitment was slower than anticipated, in February 2002, the two trials pooled their patients and used a joint monitoring and safety committee. In October 2003, the safety committee recommended that the trial be discontinued because there were 26 women in the treated group with new breast cancers compared with 7 in the non-treated group.

The HABITS trial was terminated in December 2003. Confronted with this outcome, the Stockholm investigators canceled their trial as well, even though the hazard ratio in the Stockholm patients was 0.82 (CI, 0.35-1.9).

HABITS was a randomized but not placebo-controlled trial in which hormone therapy was compared to management without hormones in women with menopausal symptoms who had been previously treated for Stage I or Stage II breast cancer.[4] Concomitant tamoxifen treatment was allowed in the HABITS patients but not aromatase inhibitors. Hormone therapy consisted of the variety of products and methods on the Swedish market, but not tibolone. Most of the treated women used products with the relatively high dose of 2 mg estradiol. After 4 years of follow-up of 442 women, there were 39 cases of new breast cancer in women using hormone therapy compared with 17 in the non-treated group for a hazard ratio of 2.4 (CI, 1.3-4.2).

The treated and non-treated groups of women in HABITS were very different in terms of characteristics and behaviors. More of the women in the treated group had hormone receptor-positive cancers (62.3%) compared with the non-treated group (54.5%). Eleven women in the treated group never received hormones; 43 in the non-treated group did receive hormones. There was a very wide range of exposure times, ranging from 0 to 80 months. About one-third of the women who received hormones changed products during the study. The method of analysis of the HABITS data was intent-to-treat, and thus the impact of these differences cannot be ascertained.

Analysis of the new breast cancers in HABITS (either local recurrences or contralateral cancers) indicated statistically significant increases only in hormone receptor-positive cancers. However, when adjusted for use of hormone therapy before diagnosis of the original breast cancer, use of tamoxifen, and hormone receptor status, the hazard ratio was 2.2 (CI, 1.0-5.1). By definition this is close, but not statistically significant.

The Stockholm trial reported in 2005, after a median follow-up of 4.1 years, 11 new breast cancers in the treated arm and 13 new breast cancers in the non-treated arm.[5] Why the difference between the Stockholm trial and HABITS? The HABITS investigators suggest that their patients had more node-positive disease, and thus "probably" had more women with subclinical disease that would be stimulated by hormone therapy. Another possibility was more protection with higher tamoxifen use in the Stockholm trial, although the HABITS trial could detect no impact of tamoxifen. The HABITS investigators believe that another possible explanation was the greater use of norethindrone and norethindrone acetate in HABITS compared with the

use of medroxyprogesterone acetate in Stockholm. All of these explanations are speculations; the difference between the two trials remains and calls into question the reliability and accuracy of the data.

The cancellation of HABITS and the Stockholm trials made it impossible for the English and Italian trials to continue recruitment in their trials, and they were also canceled. Thus, we have no ongoing clinical trials of estrogen or estrogen-progestin therapy in breast cancer survivors. In my view, the data from the Swedish trials are confusing and not definitive.

Conclusions

Although the LIBERATE trial may apply to all breast cancer survivors, speaking strictly in a scientific sense, the results were derived mainly from tamoxifen users with 10-fold fewer users of aromatase inhibitors. The possibility that estrogen or tibolone would interfere with the beneficial effects of tamoxifen or aromatase inhibitors has always been one of the objections to treating breast cancer survivors with estrogenic hormones. In a subgroup analysis of the LIBERATE trial, the group of women who had used aromatase inhibitors had a greater risk of recurrent breast cancer compared with tamoxifen; however, the CI was wide because of relatively small numbers. The authors suggest that the estrogenic effect of tibolone would be more pronounced on an occult breast cancer in estrogen-depleted tissue compared with tissue where tamoxifen was bound to the estrogen receptor and prevented estrogenic stimulation.

We don't know if the LIBERATE data are meaningful for future treatment regimens. Nevertheless, until there are new data, the use of tibolone in women with a history of breast cancer remains relatively contraindicated.

Patients and clinicians have to incorporate all of the previously mentioned experimental data into this medical decision. But when all is said and done, patients have to take an unknown medical-legal risk. Some patients will choose to take estrogen, judging the benefits to be worth the unknown risk. Until definitive data are available from clinical trials (there will be none in the near future), clinicians should support patients in this decision. Other patients will prefer to avoid any unknown risks. These patients, too, deserve support in their decision. ■

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The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

53. Which statement does *not* fit regarding the Australian study?

a. Low-level drinkers had no greater incidence of SGA.
b. The total sample of drinkers did not have a higher incidence of preterm birth.
c. There was an increase in SGA in the moderate-to-heavy drinkers, even after smoking was ruled out as a confounding variable.
d. The highest rate of preterm birth was in the binge drinkers.

54. Women saw an improvement in pain due to endometriosis after 3 months of either DMPA or implant use.

a. True
b. False

55. The following statements are true regarding tibolone *except*:

a. The local effect of tibolone is determined by target tissue of tibolone to its metabolites.
b. In normal breast tissue, tibolone lowers breast levels of potent estrogens.
c. The density of breast tissue does not change during tibolone treatment.
d. Tibolone effectively treats menopausal symptoms, but does not protect against bone loss.

Answers: 53. c, 54. a, 55. d.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■

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