Menopausal Hormone Therapy: Calculating Risks and Benefits

To the Editor:

The recent editorial by Cheryl B. Iglesia, MD,[1] was very helpful in sorting through all the data on menopausal hormone therapy. However, it is unlikely, as implied by the investigators, that the significant decline in breast cancer incidence relates to women stopping hormone therapy after the Women's Health Initiative (WHI) news in 2002 (29th Annual San Antonio Breast Cancer Symposium, December 14, 2006). Can a malignancy that takes years to manifest go away in 18 months?

Whereas breast cancer incidence increased at 1.7% each year from 1990 to 1998, it began to decrease 1% each year from 1998 to 2002.[2] By the end of 2003, there was a 7% decrease in the number of breast cancer cases diagnosed. Before July 2002, more women were using estrogens each year. In April 2006, the WHI reported a 14–35% decrease in breast cancer in the conjugated estrogen users for up to 9 years.[3] Could the increasing use of estrogen in the late 1990s be related to the decrease in new breast cancer in 2003?

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To the Editor:

I read with interest the editorial by Cheryl B. Iglesia titled "Menopausal Hormone Therapy: Calculating Risks and Benefits."[1] I have the following questions:

1. If the delay from initiation of breast cancer to diagnosis averages 6–7 years, how can a decrease in breast cancer from 2002 to 2003 related to hormone therapy be a true decrease instead of just an inability to diagnose?
2. How can the Women's Health Initiative make a similar conclusion in just 5 years of study?

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In Reply:

I would like to thank Drs. Gambrell and Natrajan for their careful reading and comments. They have suggested that the decrease in breast cancer incidence in the United States in 2003 could be attributed to the increasing use of estrogen from the mid-1990s. The proposed theory contrasts with the opinions expressed by the investigators from M. D. Anderson Cancer Center that the decrease in the incidence of breast cancer in 2003, particularly estrogen receptor–positive tumors in women aged 50–69 years, relates to the discontinuation of hormone therapy following initial publication of Women's Health Initiative (WHI) data in 2002. Furthermore, Dr. Harkins questions how a decline in estrogen plus progesterone therapy use over 1 year could result in a steep decrease in the incidence of breast cancer. Another question that therefore comes to mind is the mechanism by which unopposed estrogen can lower the risk of invasive breast cancer, since there are no data to substantiate this claim.

One can infer that the rapid discontinuation of estrogen plus progesterone or long-term unopposed estrogen use could be *associated* with a decline in breast cancer incidence, but one cannot make a definitive conclusion of *causation* in the absence of longer-term data. The answer to the question of why breast cancer incidence decreased in 2003 will remain a mystery until further analysis from the Surveillance Epidemiology and End Results (SEER) database and the WHI database is continued over the ensuing years. The investigators from M. D. Anderson Cancer have hypothesized that the rapid decline in breast cancer incidence associated with discontinuation of hormone therapy could represent either a halting of progression of clinically occult breast cancers or possible regression.[1]

In the meantime, the pattern of significant increase in risk hazard for breast cancer in estrogen plus progesterone users versus no significant increase in risk hazard for breast cancer in unopposed estrogen users has been corroborated in several randomized clinical trials (including WHI and the Heart and Estrogen/Progestin Replacement Study [HERS]), as well as in epidemiologic studies. In the absence of the requisite long-term data, practitioners must still continue to individualize therapy for symptomatic menopausal women, weighing risks of cancer and adverse cardiovascular events compared with benefits in quality of life from relief of vasomotor and vulvovaginal symptoms.

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Nuchal Translucency and the Risk of Congenital Heart Disease

To the Editor:

The FASTER (First and Second Trimester Evaluation of Risk) Research Consortium reported that the sensitivity of screening for congenital heart defects by nuchal translucency is 15.4% for a screen-positive rate of 1.6%.[1] The reason for this low sensitivity, which is much lower than in previous studies,[2] is the decision by the authors to exclude a subgroup of fetuses

with high nuchal translucency by arbitrarily calling them cystic hygromas.[3]

In the FASTER data set of 38,167 screened patients, 134 fetuses were defined as having a cystic hygroma. In 65 of these 134 cases, the fetuses were euploid, and 22 of these were reported as having major structural fetal malformations. Although the description is incomplete, 16 of these major defects were defined as being cardiac in nature.

Consequently, in the FASTER study the actual sensitivity of screening for major cardiac defects by nuchal translucency was 35.3% (24 of 68) rather than the reported 15.4% (8 of 52). This is similar to the 37% sensitivity in a meta-analysis of studies examining the screening performance of nuchal translucency thickness for the detection of cardiac defects in fetuses with normal karyotype.[2]

One of the cardinal rules of scientific investigation is to hold as many parameters similar as possible, allowing comparisons between studies. For reasons that are not entirely clear to the rest of the world, the FASTER consortium has developed a number of definitions that differ from those commonly used, such as distinction between high nuchal translucency and cystic hygromas,[3] and has devised a novel set of criteria for defining "major" defects. This practice not only removes our ability to make such comparisons but also potentially takes credibility away from what may otherwise be a well-designed study. We urge the authors to cease this practice and submit further analysis of their data, which addresses these issues.

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In Reply:

We thank Dr. Hyett and colleagues for their letter. In the Discussion of our article, we clearly acknowledge that the exclusion of septated cystic hygromas in our study design may in part explain the lower screening performance of nuchal translucency for major congenital heart disease observed in our study.[1] Assuming all cystic hygroma cases reported separately had nuchal translucency measurements of 2.0 multiples of the median or greater and all cardiac lesions were major, then as Hyett and colleagues point out, the sensitivity of screening for major cardiac defects as defined in our study was 35.3%.[1,2] However, direct comparisons between previously published studies are fraught with difficulties, as many do not report on whether cases of cystic hygroma were included or excluded in the analysis or clearly classify cardiac lesions as major or minor in the methods.[3,4] Based on our data, even including all cases of cystic hygroma and all cardiac anomalies (patent foramen ovale and patent ductus arteriosus not classified as congenital heart defects), the sensitivity of nuchal translucency for congenital heart defects in a large, unselected population remains low at 14.6% (35 of 240).[1,2]

Despite the promising findings of Hyett's initial study, subsequent studies have been unable to replicate their results.[1,3] We theorized that this may in part be due to its retrospective nature, high-risk population, inclusion of cystic hygromas, and lack of extended follow-up. One may argue whether a distinction between first-trimester cystic hygroma and nuchal translucency should be made, but it is our opinion that this will be done routinely in clinical practice. Septated cystic hygromas are easily recognized at the time of first-trimester assessment, and these patients will be counseled and managed differently due to the increased risks of aneuploidy, associated anomalies, and adverse outcomes.[2] Therefore, it is clinically useful to have septated cystic hygromas and enlarged simple nuchal translucencies evaluated and reported separately even though both warrant investigation for fetal aneuploidy and associated anomalies such as congenital heart disease.5

The classification of major and minor congenital heart lesions used in our study was developed in consultation with our pediatric cardiology colleagues and follows the suggested grading of congenital heart disease detectable prenatally.[6] Unfortunately, there is a lack of consensus on the definition of major congenital heart disease.[7] We based our definition of major heart defects on whether they were suitable for screening–those "associated with poor perinatal outcome or those with the potential to be ductal-dependent after birth or both. These included heart defects with risk of significant neonatal morbidity and mortality or need for surgical correction in infancy."[1] We did not feel that minor lesions such as atrial septal defects, small ventricular defects, and mild valvular stenosis that have favorable perinatal outcomes and are not commonly detected prenatally should be targeted for screening. In a recent publication on cardiac defects and nuchal translucency coauthored by Dr. Nicolaides, "cardiac defects are considered to be major if they require surgery or interventional cardiac catheterization within the first year of life."[8] It is clear that further refinement and perhaps standardization of the definition of major congenital heart disease is needed.

These considerations, septated cystic hygromas and classification of congenital heart defects, were addressed during the design phase of the FASTER trial and are clearly described in our publications.[1,2] Based on our results, we conclude that nuchal translucency does not appear to be a good screening tool for congenital heart disease although it is a marker and warrants referral for fetal echocardiography if identified at the time of first-trimester screening for aneuploidy.

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Effects of Teamwork Training on Adverse Outcomes and Process of Care in Labor and Delivery: A Randomized Controlled Trial

To the Editor:

I commend Nielsen and colleagues[1] for their randomized controlled trial evaluating the effect of teamwork training on the occurrence of adverse outcomes and process of care in labor and delivery units of seven hospitals. Outcome-based evaluations are absent for most Crew Resource Management training applications in health care as well as in other industries. However, the authors' conclusion is premature, and their findings lack the external validity to generalize their conclusions about the effectiveness of Crew Resource Management training to other programs.

Salas and colleagues[2] did an exhaustive review of the literature on the evaluation of Crew Resource Management training in 2001 (58 studies), with an update in 2006 (28 additional studies). Salas employs the Kirkpatrick framework[3] for training evaluation at four levels: 1) Reaction–did they like it? 2) Learning–what did they learn? 3) Behavior–did their behavior change? 4) Organizational Impact–measurable safety outcomes? Salas concludes their recent review by calling for multilevel program evaluations to determine Crew Resource Management program effectiveness. The question remains open.

Nielson and colleagues describe an evaluation of a "train-the-trainers" Crew Resource Management program based upon their Adverse Outcomes Index. What is missing in their analysis is whether specific behaviors changed among the subjects in their intervention arm. Without evidence for behavioral change following Crew Resource Management training, the conclusions by this group cannot be supported.

The Crew Resource Management–based Medical Team Training program offered by the VA National Center for Patient Safety is driven by a small group of physicians and nurses that deliver the program to clinicians with preparation and follow-up spanning a minimum of 14 months for each facility. We are employing a multilevel program evaluation, as recommended by Salas, using survey data assessing reaction to the Learning Sessions, the Safety Attitudes Questionnaire (before and after) to assess learning, follow-up semistructured interviews for 1 year to capture behavioral change, and the All Employee Survey Job Satisfaction Index plus VA surgical outcome data to assess organizational impact. Although anecdotal reports from participating VA Medical Centers are encouraging, it is far too early to judge the effectiveness of our program, just as it is premature to conclude that a Crew Resource Management program is ineffective without a multilevel evaluation.

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To the Editor:

We were pleased to read "Effects of Teamwork Training on Adverse Outcomes and Process of Care in Labor and Delivery: A Randomized Controlled Trial"[1] by Nielson et al. We commend the authors for undertaking a randomized controlled trial with adequate power and trained data coordinators. The authors conclude that medical team training, as implemented in this study, was ineffective at reducing adverse obstetric outcome. While we agree with this conclusion, we believe that it is premature to discount medical team training.

Of primary concern is the fact that there is no description of whether or not staff behaviors actually changed in response to team training. Since the intervention consisted of a single educational session, it is not surprising that only minor differences were noted after the intervention. Because changing behavior is complex, it is unlikely to occur in the absence of ongoing follow-up, encouragement, and feedback.

An additional concern is the fact that a single intervention is unlikely to lead to ongoing improvement. As demonstrated by the Northern New England Cardiovascular Disease Study Group,[2] sustained improvement takes concentrated, coordinated effort over time. Specific outcomes must be targeted and the processes that underlie them understood. Data collection and reporting must be carried out in ways that are meaningful to frontline work-

ers, and this is best accomplished using Statistical Process Control. It is likely that improving obstetric outcomes will require a similar approach. If such a model is adopted, we strongly advocate for use of Statistical Process Control methods because, although the Obstetric Adverse Outcome Index seems appropriate in a research setting, from a quality improvement perspective it is problematic. Highly aggregated data becomes disconnected from frontline workers and from the processes of care and may actually inhibit improvement efforts.

In conclusion, we feel it is premature to conclude that teamwork training has no role in obstetric quality improvement. We advocate for measuring actual implementation of the tools taught in the training and further research to delineate which processes of care, if any, are amenable to improvement with team training. Once the authors are confident that they have changed behavior on labor and delivery, it would then be appropriate to target those previously identified processes for improvement and to collect data over time to evaluate the success or failure of improvement efforts.

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In Reply:

We thank Dr. Dunn and Dr. Mooney and Ms. Neily, RN, for their comments. Both raised concerns about whether specific behaviors changed among the trained personnel in the intervention arm following a single educational session and felt that the absence of documenting change in behavior may have led to a premature conclusion that Crew Resource Management training was ineffective. Budgetary and time constraints precluded behavioral observations in the seven intervention and eight control hospital labor and delivery units and use of a four-level training evaluation such as the Kirkpatrick framework.

We do not feel that our study discounts Crew Resource Management training as ineffective, but rather implies that a longer implementation period is likely necessary to demonstrate both changes in behavior and improvements in processes and outcomes. Personal experience from the authors at both Madigan Army Medical Center and Beth Israel Deaconess Medical Center indicate that behavior change in staff and processes on labor and delivery may take up to 1 year or more to effectively implement and sustain. The experience of Crew Resource Management in aviation and teamwork training in other industries has led many organizations to pursue development of more complex teamwork training models, including the recently released TeamSTEPPS program, developed jointly by the Department of Defense and the Agency for Healthcare Research and Quality.[1,2] These models focus on cultural change, implementation strategies, and customized sustainment plans.

Precise measures of quality and adverse outcomes are required to completely evaluate the effects of Crew Resource Management in obstetrics. We acknowledge that our creation of the Adverse Outcome Index as an aggregated data set of outcomes may not be a perfect tool to assess obstetric outcomes. However, since adverse outcomes in obstetrics are rare, and precise and uniformly accepted definitions of quality obstetric care are lacking, we feel this tool should be considered for possible validation as a quality improvement measure as we further evaluate the effects of Crew Resource Management. As we discuss in the paper, with knowledge of the intracluster correlation coefficient and Adverse Outcome Index observed in our study, future cluster-randomized trials will be able to provide significant new evidence on the effectiveness of Crew Resource Management training in quality obstetric care.

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Human Uterus Retrieval From a Multiorgan Donor

To the Editor:

Surgical techniques for uterine transplantation may become routine. The concern we have with studies on pregnancy outcomes posttransplantation[1] is that they downplay the effects immunosuppressant drugs have on fetal health. The authors stated that fetal risk posttransplant appears acceptable based on the low numbers of malformations in self-reported data from essential organ transplants. Although authors of similar human studies noted an increased rate of combined therapeutic and spontaneous abortions and stillborns (ie, non–live births), the focus was on the low rate of birth defects, where "malformation risk in their newborns did not seem to be significantly different from the general population rate."[2] Given the increased rate of non–live births, the evaluation of immunosuppressant drugs should not be based solely on fetal malformations.

Of 11 commonly used immunosup-

pressant drugs,[2] nine are Pregnancy Category C (ie, uncertain safety; no human and animal studies) or D (ie, unsafe; evidence of fetal risk). In transplant studies, reasons for the high rate of non–live births were not given[2] or not included in the analysis.[3] Also, none of the referenced animal studies of pup births posttransplantation[4] used immunosuppressant drugs. Immunosuppressant drugs may have played a key role in the increased rate of human non–live births. Expecting to have data from animal posttransplantation birth studies using Pregnancy Class C and D immunosuppressant drugs is reasonable. Future publications should not get too ahead of the unresolved issue of immunosuppressant drugs' influence on fetal health. Guaranteed, couples who go through a uterine transplant procedure to have a child will want to know this information.

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In Reply:

We appreciate the thoughtful comments of Drs. Burnett and McDonald and agree that uterine transplantation may someday become routine. However we disagree with their description of the safety of pregnancy in organ transplant recipients and question the relevance of "non–live births" in otherwise infertile patients.

Successful pregnancies have been reported since the 1960s. A PubMed search using the term "pregnancy organ transplantation" resulted in 229 articles covering every aspect of pregnancy in transplant recipients. Many others are also available.

Information to date suggests that immunosuppressive medications are relatively safe to use during pregnancy.[1] "Relatively safe" does not, cannot, and will never mean "entirely safe." It does mean that the results of using these essential drugs in pregnancy compare "relatively" well with normal pregnancy outcomes, including rates of preterm birth, premature rupture, and low birth weight.[1] They also compare well with other assisted reproductive technologies and other high-risk pregnancies. Cyclosporine A does not appear to be a major human teratogen.[2] Congenital anomalies reported in the fetuses exposed in utero are comparable with the nonexposed fetuses in the general population. Fetuses exposed in utero with azathioprine have no clear pattern of congenital anomalies.

Additional animal data may not be reliable or improve pregnancy outcomes, but we continue to use these models seeking any possible patient benefit. Unfortunately, there is no perfect or sufficient preclinical nonhuman model. However, the large amounts of currently available human studies are reassuring in counseling pregnant transplant patients. The Food and Drug Administration Use-in-Pregnancy Categories should not determine clinical practice. They are arbitrary and inconsistent.[3,4]

Although there is little specifically on pregnancy loss in transplant recipients, the available data does not prove an increase in non–live births. Both the numerator and denominator are highly biased by selection and reporting issues. For women with no other option, a theoretical increase in non–live births is not a valid concern when considering fertility restoration through uterus transplantation or any other organ transplant.

The safety of both the mother and future child must be considered in balancing the risk of uterus transplantation. For the uterine transplant recipient, assuming the risk herself of bearing a child compares favorably with the risk assumed by a paid surrogate, women undergoing assisted reproductive technology, and pregnancy with serious comorbidities. The uterine transplant recipient must uniquely assume the added risk of short-term immunosuppression. However, a mother often chooses to compromise her health for the benefit of her child. Pregnancy is inherently a dangerous undertaking and is still responsible for hundreds of thousands of deaths each year throughout the world. The final arbiter of "relatively safe" is an informed, autonomous patient with a supportive physician. In this context, 9 months or more of immunosuppression is not an excessive risk for the transplant recipient in pursuit of a child.

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