Gynecologists and Estrogen

an affair of the heart

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ABSTRACT Although definitive studies have shown that hormone therapy in menopausal women has no overall or cardiovascular health benefit, obstetrician-gynecologists continue to believe that estrogen benefits women's health. This mistaken belief may stem from cultural factors unique to obstetrics and gynecology, as well as from the dependence of physicians on pharmaceutical companies for the provision and interpretation of scientific information.

DESPITE AN OVERWHELMING AMOUNT of evidence to the contrary, many physicians still believe that estrogenic hormones have overall health benefits. In this essay, we describe both stasis and change in physician beliefs about estrogen and explore some cultural factors within obstetrics and gynecology that may render that specialty especially susceptible to views that are not supported by data.

History

In 1947, Premarin (conjugated equine estrogens) became the first hormone therapy (HT) approved by the FDA for the treatment of hot flashes. In the 1960s,

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estrogen was promoted as a youth-preserving treatment; a vigorous advertising campaign aimed at physicians was fortified by the publication of a pharmaceutical company–funded book, *Feminine Forever*, written by the gynecologist Robert Wilson (1966) and aimed at consumers. *Feminine Forever* promised that estrogen would restore youth, health, beauty, and tractability to menopausal women: "Menopausal symptoms, such as weakening of the bones, dowager's hump, gastro-intestinal disorders, heart trouble, hardening of the arteries, atrophy of the breasts and sexual organs, disturbed vision, wrinkling of the skin, pains in the joints, etc, can be avoided by premenopausal therapy and often cured by postmenopausal therapy." The possible risks of estrogen were dismissed: "The myth that estrogen is a causative factor in cancer has been proven to be entirely false. On the contrary, indications are that estrogen acts as a cancer preventive. Certainly the continuation of regular menstruation throughout life has a healthful cleansing effect on uterine tissues and seemingly reduces the incidence of endometrial cancer."

Premarin was widely prescribed in the 1960s but fell out of favor in the mid-1970s, after it was shown to increase rates of endometrial cancer eight-fold. HT was resurrected in the 1980s, when combination products were introduced; progestins were added to counter estrogen's proliferative effects on the endometrium. The revamped version of estrogen was promoted for menopausal health.

Estrogens are effective treatment for hot flashes but have always been prescribed for other reasons. Sales of estrogen-progestin products soared through the 1980s and 1990s. In 1986, 20.3 million prescriptions for noncontraceptive hormones were dispensed, 66 to 82% for menopausal HT (Hemminki et al. 1988). Prescriptions for menopausal HT increased to 58 million in 1995, and then rose further, to 90 million a year, between 1999 and June 2002 (Hersh, Stefanick, and Stafford 2004). The increasing rate of hormone prescriptions cannot be explained by an increase in the number of menopausal women or menopausal symptoms.

Gynecologists have always been the primary prescribers of HT in the United States and other countries. Gynecologists may be more likely to see women with hot flashes than other physicians; nonetheless, a survey carried out in the early 1990s found that HT prescription rates for symptomatic women were similar among specialties. Gynecologists, however, were almost four times as likely as internists or family practitioners to prescribe hormones to women without symptoms (Stafford et al. 1997). In the United States in 2002, gynecologists wrote 70% of estrogen or estrogen-progestin prescriptions. A cross-sectional survey of 426 postmenopausal women in Iowa found that women who were patients of gynecologists were 2.6 times more likely to receive estrogens than were women who were patients of family practitioners (Levy et al. 2003). The belief that hormones promote health is not limited to the United States. In Estonia and Finland, gynecologists are also more likely than family practitioners to believe that all menopausal women should be offered hormones (Hemminki 2004).

Until very recently, menopausal HT was termed "hormone replacement therapy" (HRT), or estrogen replacement therapy (ERT), if estrogen was used without a progestin. This terminology implied deficiency. Gynecologists were targeted by hormone manufacturers, who encouraged physicians to view the naturally lower levels of estrogen in older women as an endocrine disorder, similar to diabetes mellitus or hypothyroidism. Gynecologists are more likely than family practitioners or internists to view menopause as an endocrine deficiency (Saver et al. 1997; Stafford et al. 1997), perhaps because gynecological literature is replete with statements such as:

> Nevertheless, more than enough evidence does exist to define the climacteric as an endocrinopathy in which changes in hormonal profile are associated with extensive pelvic and extrapelvic target tissue effects. (Utian 1987)
>
> In recent years, there has been increasing recognition that ovarian failure and the resultant postmenopausal syndrome represent an endocrinopathy. (Stumpf and Trolice 1994)
>
> Menopause is a pivotal time for all women, with subsequent health consequences affecting society as a whole, so every effort should be invested in favorable intervention during this period. Endocrine aging in women is accompanied by certain serious structural, metabolic, and functional health outcomes. Certain conditions are reversible with HT, and it is therefore legitimate to value HT as a pure antiaging therapy. (Shoham and Kopernik 2004)

HORMONES AND HEALTH PROMOTION

By the early 1990s, pharmaceutical company efforts convinced gynecologists that estrogens prevented cardiovascular disease, although not a single randomized clinical trial with disease endpoints had ever been performed in women. The only randomized controlled trial of estrogen to prevent cardiovascular disease to date had been done in men; the Coronary Drug Project was stopped early because estrogen increased cardiovascular events (Stamler 1977). The belief that estrogen would benefit women was based on evidence that is not scientifically reliable for prescribing decisions. First, estrogen was observed to decrease total and LDL cholesterol, and to increase HDL cholesterol. Second, estrogen appeared to have antioxidant effects. Third, estrogen was associated with decreased arteriolar constriction. Fourth, estrogen treatment of experimental animals on high-fat diets appeared to prevent manifestations of vascular damage. Finally, several, though not all, observational studies had shown that women with cardiovascular disease were less likely to have used menopausal HT than women without cardiovascular disease.

None of this constituted proof that estrogen prevented heart disease in women. In fact, in 1990 when Wyeth-Ayerst, the manufacturer of Premarin and Prempro (equine estrogen 0.625 mg with medroxyprogesterone acetate 2.5 mg),

sought FDA approval for a labeling change stating that Premarin prevented heart disease, the application was appropriately denied. Clinical studies of cholesterol or other surrogate markers cannot prove that a therapy reduces cardiovascular risk. Observational studies can never prove therapeutic effectiveness, because the choices that distinguish groups may be markers for other choices or circumstances that affect disease risk.

Data supporting the fact that women who chose to take estrogen were different from women who chose not to were available in the medical literature in the 1990s. Estrogen users had fewer cardiovascular risk factors than non-estrogen users prior to therapy and were more likely to make lifestyle changes that reduced cardiovascular disease risk than were non-users (Barrett-Connor 1991; Egeland et al. 1988; Kritz-Silverstein and Barrett-Connor 1996).

Despite the lack of reliable evidence supporting estrogen's purported cardiovascular benefits, gynecologists believed that HT was more important for preserving health than smoking cessation. A survey asked 330 gynecologists, family practitioners, and general internists in Washington, Alaska, Montana, and Idaho to rank the importance of discussing eight disease prevention issues. Gynecologists ranked mammography first and HT second, while family practitioners and internists ranked smoking cessation first (Saver et al. 1997). The sincerity of gynecologists' belief in estrogen can be demonstrated by the fact that women gynecologists were more likely than other practitioners to use HT themselves (Frank and Elon 2003; McNagny, Wenger, and Frank 1997).

Gynecologists also minimized risks attributed to HT. A 1997 survey of managed care providers in North Carolina found that gynecologists were less concerned about the potential link between HT and breast cancer or thromboembolic events than were family practitioners or internists (Exline, Siegler, and Bastian 1998); another study found that gynecologists were significantly less likely to express concern about thromboembolic risk than other physicians (Rolnick et al. 1999).

The perceived strength of the evidence of benefits was so great that gynecologists believed that all menopausal women should be informed of the benefits. A 1992 Technical Bulletin of the American College of Obstetricians and Gynecologists (ACOG) stated that although no large randomized drug trials had been conducted, "epidemiologic studies . . . strongly suggest that hormone replacement therapy decreases the risk of cardiovascular disease." In May 1998, ACOG strengthened its recommendation:

> Traditionally, hormone replacement therapy has been started in menopausal women for treatment of vasomotor symptoms, mood disturbances, vaginal dryness, and osteoporosis prevention. However, because an increasing number of menopausal women are now better informed regarding menopausal changes and are beginning to embrace the concept of preventive health care, other additional benefits of hormone replacement therapy such as protection against cardiovascu-

lar disease and possible protection or delay in the onset of senile dementias make this option even more appealing.

By the end of the 20th century, some practitioners in other specialties were swayed by the mounting promotion of menopausal estrogen therapy. A survey of 260 gynecologists, family practitioners, and general internists found that all groups believed that menopausal estrogen benefited cardiovascular disease and osteoporosis. Gynecologists, however, were significantly more likely than other physicians to believe that HT benefited Alzheimer's disease (Rolnick et al. 1999).

RANDOMIZED CONTROLLED TRIALS OF HT FOR DISEASE PREVENTION

The first major challenge to the premise that estrogen was cardioprotective was the Heart and Estrogen/Progestin Replacement Study (HERS), a prospective, randomized, double-blind study in 2,763 women with coronary disease. Women with previous heart attacks or severe cardiovascular disease were chosen because this group was anticipated to benefit most. HERS was a secondary prevention study, a study that treats subjects at high risk of whatever disease outcome is being studied. (In contrast, primary prevention studies test interventions in the general population.) HERS found no benefit of hormones in preventing cardiovascular events at five years or at 6.8 years (Grady et al. 2002; Hulley et al. 1998).

Physician speakers, most of whom were paid by pharmaceutical companies, were quickly dispatched to explain to gynecologists that estrogen was still expected to benefit healthy women, and that even women with heart disease would have benefited had HERS lasted longer:

> The results of HERS do not contradict the weight of epidemiological study findings showing a primary protective CVD effect in longer-term HRT users. Indeed, because of possible serious flaws in the study, a protective benefit of HRT for secondary CVD prevention cannot be ruled out. The HERS findings actually support the beneficial changes in lipoprotein profiles noted in the majority of studies, and they confirm the well-established benefit on CVD in long-term HRT users. (Thorneycroft 2001)

The hormone-treated group in HERS showed more cardiovascular events in the first and second year, but fewer events in the fourth and fifth year, so hormone proponents recommended that women continue treatment in order to experience the late-occurring benefits. This argument was disingenuous. Cumulative events were similar in the hormone and the placebo group; the way women avoided having cardiovascular events in the fourth and fifth years was by having these events in the first or second year. The net effect of HT was not to decrease cardiovascular events, but rather to hasten them.

Gynecologists remained committed to estrogen. In 2000, a survey of 250

gynecologist members of the North American Menopause Society and 250 members of an Israeli menopause society found that 94.6% of the American gynecologists recommended HT during menopause unless the treatment was specifically contraindicated; rates of hormone recommendation were similar among Israeli gynecologists (Kaplan et al. 2002). Another international study, also conducted after HERS was reported, surveyed U.S. and European authors of articles on HT and cardiovascular disease. Thirty-seven of 108 authors, representing gynecologists, cardiologists, internists, and nonphysician scientists, responded. Asked to consider a risk modification of more than 20% as clinically relevant, 57% of responders still thought that HT was beneficial for primary prevention, and about 30% thought it was beneficial for secondary prevention (Rozenberg, Fellemans, and Ham 2001). Not one of the respondents believed that HT could have an unfavorable effect (increasing risk 20%) on primary prevention, and only 2% thought it could have an unfavorable effect on secondary prevention.

The definitive study of hormone use in healthy postmenopausal women was in progress at the time. As a consequence of activist efforts by the National Women's Health Network, a consumer advocacy group, the National Institutes of Health (NIH) designed and funded the Women's Health Initiative (WHI), a large, prospective, randomized placebo-controlled trial of estrogen (with and without progestin) in healthy menopausal women. In July 2002, the combined estrogen-progestin arm of the WHI was stopped early because the treated group experienced higher rates of breast cancer, cardiovascular disease, and an increased index of overall harm (Writing Group for the Women's Health Initiative Investigators 2002). In February 2004, the estrogen-only arm was halted early because of an increase in stroke among the treated group, and because estrogen failed to show any cardiovascular benefit. Later analyses showed that the estrogen-progestin combination doubled the risk of venous thrombosis and dementia (Cushman et al. 2004; Shumaker et al. 2004); representatives from NIH have stated that a trend towards increased dementia risk has also been noted in the estrogen-only arm.

WHI was a large, primary prevention trial that contained enough subjects (more than 27,000) to answer the research question; used a design widely acknowledged to be the standard in testing therapeutic efficacy; tested Prempro, the most popular hormone combination; and was monitored by a data safety monitoring board using pre-established criteria. Practitioners should have been satisfied that the question of estrogen as a health-protecting drug had been resolved. Instead, a storm of protest erupted from physicians who could not, or would not, believe the results. Objections to the WHI results (almost exclusively from gynecologists) were so widespread that the media characterized the WHI results as confusing and controversial.

In truth, there was no confusion about the data, which were monotonously consistent with HERS and other randomized controlled studies.

SPINNING THE WHI RESULTS

In the three years since July 2002, menopause "experts," almost all of whom receive money from companies that sell HT products, have repeatedly written or lectured about the failings of the WHI. The fundamental theme throughout these arguments is that the women in the WHI were not normal, did not represent typical patients, and were not the sort of women likely to benefit from estrogen. Diverse versions of this argument were often combined to mimic an accumulation of evidence. Here are the most common arguments used in an attempt to refute the WHI findings.

Too Few Participants Close to Onset of Menopause

The first argument is that the WHI contained too few women close to the onset of menopause:

> The WHI was a study of elderly women who were not representative of the population receiving hormone therapy. (Speroff 2003)

> However, participants were not typical users of HRT. Women enrolled were asymptomatic and older (mean 63 years) than many women who take HRT (commonly in their early 50s). (Grimes and Lobo 2002)

This argument is based on the premise that estrogen prevents menopause-related illness, but only if therapy is started early, that is, before decrepitude has set in. The fundamental premise is false: there is no evidence that the onset of menopause is associated with ill health. Besides, more than 9,000 of the women (fully a third) in the WHI were in their 50s. In fact, the WHI is the largest randomized controlled trial ever done of women in this age group. Moreover, age and years since menopause made no independent contribution to the WHI results (Manson et al. 2003). In other words, estrogen did not prevent cardiovascular disease in younger menopausal women any more than it did in older women.

Asymptomatic Women Are Not Normal

The second common argument is that women in the WHI were not having menopausal symptoms, so were not normal:

> Women with significant menopausal symptoms were excluded from the study to avoid an exceedingly high dropout rate in the placebo group. For this reason, less than 10% of the subjects were close to their age of menopause (the number is probably even smaller). (Speroff 2002a)

> One of the major exclusion criteria in the WHI was that women unable to take placebo due to menopausal symptoms, such as hot flashes, were excluded from the trial. It is relevant to note, however, that flushing due to menopausal symptoms may indicate potential responsiveness of the vascular wall to estrogen therapy. (Hodis 2002)

Purveyors of this argument seem to imply that women close to menopause who are not having hot flushes are aberrant. In fact, many women have no menopausal symptoms, or the symptoms are not bothersome. Only a minority of women who began HT before WHI cited hot flashes as the reason for starting (Salamone et al. 1999). The mistaken belief that all normal menopausal women have severe hot flashes is popular in the United States. At a recent conference for gynecologists, an audience member asked one of us whether a menopausal woman without hot flashes should undergo testing for excessive estrogen levels, in order to identify those with hormone-producing neoplasms.

Women with very severe menopausal symptoms (especially hot flushing) were excluded from the WHI in order not to deny them effective therapy, but some women in the WHI did have hot flashes. At baseline, 12.7% of the treated group and 12.2% of the placebo group had moderate or severe hot flashes or night sweats (Hays et al. 2003).

The insinuation that hot flushes, as a marker of so-called vasomotor instability, characterize women whose cardiovascular systems are the most likely to be rescued by estrogen therapy is physiologically unsupported.

Preexisting Cardiovascular Disease

Another claim is that the women in the WHI had preexisting cardiovascular disease:

> . . . this study was not a primary prevention study of cardiovascular disease, but a study of older women that undoubtedly already had a significant degree of atherosclerosis. (Speroff 2002a)

> The population in the Women's Health Initiative trial may have already developed substantial atherosclerosis and thus may not have been able to respond to HRT. (Grimes and Lobo 2002)

> I believe a theme has emerged from the epidemiologic confusion of last few years: It takes healthy tissue to allow effective responses to estrogen and to maintain health. (Speroff 2003)

> In terms of basic physiology, it appears that women in the older age group have some degree of atherosclerosis, although they are not clinically symptomatic. . . . Thus, characterizing the study group as "healthy postmenopausal" women may not be adequate. In other words, the WHI was not a true primary but a secondary prevention trial in terms of cardiovascular study. (Kopernik and Shoham 2004)

Hormone proponents had previously attempted to neutralize HERS by arguing that the arteries of women with cardiac disease were too damaged to respond to estrogen. This argument led to the recommendation to start hormones during the years prior to cardiac compromise, early in menopause.

The WHI, a primary prevention trial, was designed to assess the effect of treat-

ment on the cardiovascular risk of women who had never had a heart attack, stroke, breast cancer, or any other of the outcomes studied. When the WHI dashed the theory that healthy women benefited from estrogen, critics rather desperately suggested that, appearances and inclusion criteria to the contrary, the women in the WHI weren't actually healthy. There must be something wrong with women who don't benefit from estrogen. As one researcher put it: "The population of the WHI study was described as old, overweight, smoking, and ill" (Hemminki 2004).

The claim that women in the WHI represented a secretly sick population is untenable. The fact that participants in clinical trials are healthier than the general population is so well documented that the phenomenon has been named the "healthy volunteer effect" (Froom et al. 1999; Lindsted et al. 1996). Consistent with the healthy volunteer effect, WHI participants in both the estrogen-progestin and placebo groups had rates of cardiovascular disease lower than in the general population. In terms of cardiovascular risk factors, women in the WHI actually represented the general population quite well. Among women assigned to hormones, a third were obese, 36% of women had hypertension, and 49% were current or past smokers. It is likely that some women in both the hormone and placebo groups did, indeed, have underlying cardiovascular disease. But the women in the WHI accurately represented the very women who had been targeted to receive menopausal estrogen. Prior to WHI (and since WHI, for that matter), no one has suggested a normal coronary angiogram as a prerequisite for estrogen therapy.

Participants Not on Hormones Long Enough to See Benefit

Another argument is that the women in the WHI were not on hormones long enough to see a benefit:

> The WHI study has been the largest long-term, placebo-controlled, randomized trial of HT. It is of extreme importance to the reproductive medicine community, and there has been immense interest in the findings. This study has provided data that could previously only be estimated from observational studies. . . . however, the study was terminated prematurely, because the results had crossed the threshold for adverse outcome. (Kopernik and Shoham 2004)

HERS showed more cardiovascular events in the first and second year and fewer in the fourth and fifth year. Results in the WHI were nearly identical: the greatest risk for cardiovascular events in women on estrogen was during the first year. Just as in HERS, the WHI showed an apparent shifting of events from later years into the early years of hormone exposure. Recycling an argument used to dismiss HERS, some argued that the WHI ended prematurely, and that had it been permitted to continue, the elusive long-term cardioprotective benefits of estrogen would have materialized (Shoham and Kopernik 2004).

Aside from the unsupported nature of this assertion, at the time the WHI was stopped for safety reasons, the investigators calculated that even a 50% decline in cardiovascular events in women taking hormones (the most optimistic claim prior to the WHI) beginning the moment the trial was stopped would have failed to be statistically significant. Continuing the study would not have allowed later-year benefits to become apparent because there are no later-year benefits. At best, hormonal therapy is a kind of cardiovascular fitness test: a woman who survives the first few years of therapy is less likely to die of a myocardial infarction in later years.

Despite an average follow-up of 5.2 years in the discontinued arm of the WHI, it has been claimed that the WHI did not address long-term risks (Berga 2002). The WHI was stopped after interim analysis by a safety monitoring board, using predetermined criteria. The trial was stopped because statistical boundaries were crossed for breast cancer and for overall harm. The research question had been answered. There was no ethical basis for continuing the study. The predetermined adverse event criterion was a lower bound of 95% confidence interval around risk estimates reaching unity. In other words, the study designers decided that the study would be stopped when overall harm was shown at $P = 0.05$, rather than $P < 0.05$.

Dropouts Render Results Uninterpretable

Finally, opponents claim that there were so many dropouts that the WHI trial results are uninterpretable: "Finally, the intention-to-treat analysis, a method preferred for clinical trials, is handicapped by the high dropout rates in both the treated and placebo groups" (Speroff 2003). Dropout rates that are dissimilar between study groups could skew results, but dropout rates were similar between groups in the WHI (42% in the estrogen-progestin group, and 38% in the placebo group). Additionally, this number is similar to, perhaps even lower than, the dropout rate among hormone users in the community. In a retrospective analysis of 29,718 new HT users, 54.4% were nonadherent after one year (Faulkner et al. 1998). In 604 women over 65 years of age, 62% discontinued HT within 12 months; among 866 women aged 50 to 55 years, 48% discontinued HT within 12 months (Ettinger, Pressman, and Silver 1999).

PRESCRIPTION AND PROMOTION

In the wake of the WHI results, prescriptions for menopausal estrogen products declined dramatically. In the six months following the July 2002 announcement that the estrogen-progestin arm of the WHI had been stopped for safety reasons, prescriptions for Prempro in the United States dropped by 66%, and those for Premarin by 33%; since that time, small increases have been seen in vaginal formulations and low-dose Prempro (Hersh, Stefanick, and Stafford 2002). By the fourth quarter of 2003, prescriptions of Prempro had dropped 80%, compared to

the second quarter of 2002 (Majumdar, Almasi, and Stafford 2004). The decrease in prescriptions appears to closely track decreased promotional spending, which declined 61% for Prempro during the same period. The only hormone preparations for which prescriptions increased (lower-dose Premarin and Prempro) were the only preparations for which promotional spending increased (Majumdar, Almasi, and Stafford 2004).

After the estrogen-progestin arm of the WHI was halted, hormone supporters rushed to absolve estrogen from blame. Estrogen was beneficial, it was argued; progestin was the problem (*Contemporary Ob-Gyn* 2002). This hope was dashed when the estrogen arm of the WHI was stopped and showed no cardiovascular benefit from estrogen-only therapy. In fact, there was adequate RCT evidence prior to the cessation of the WHI that estrogen alone (and non-equine estrogen at that) was without cardiovascular benefit. A randomized placebo-controlled trial tested 17,-estradiol in 664 postmenopausal women after a recent stroke or transient ischemic attack and found no differences between groups in fatal or nonfatal strokes, other cardiovascular events, or death (Viscoli et al. 2002). The Estrogen Replacement and Atherosclerosis (ERA) study, in 309 women with angiographically confirmed coronary disease, showed no benefit of either estrogen-progestin or estrogen alone in preventing progression of atherosclerosis (Herrington et al. 2000). Another prospective randomized trial of 293 women with unstable angina found no benefit of intravenous estrogen followed by three weeks estrogen-progestin or conjugated estrogen alone on ischemic events in women with unstable angina (Schulman et al. 2002).

The most recent and most definitive study, the Estrogen in the Prevention of Reinfarction Trial (ESPRIT), randomized 1,017 postmenopausal women with a previous myocardial infarction to unopposed estradiol valerate 2 mg or placebo for two years; only women who experienced vaginal bleeding and an abnormal uterine biopsy were given progestin (Cherry et al. 2002). There was no difference between groups in frequency of reinfarction or death.

After a suitable period of mourning, pharmaceutical companies may begin overpromoting different lower-dose, transdermal, vaginal, or otherwise revamped hormonal drugs. A prominent current argument is that the WHI tested the wrong drug. Prempro, however, was by far the most widely used HT in the United States when the WHI was designed (and reported). Moreover, the tested product was the formulation for which benefit had been claimed in observational studies.

Since the WHI results were released in 2002, almost no articles supporting the use of HT for cardioprotection have appeared in internal medicine and family practice journals. Gynecology publications, on the other hand, regularly feature articles that attack the reliability of the WHI data, dismiss all evidence from RCTs, or assert the validity of practicing medicine based on the intuition of "experts," or "eminence-based medicine" (Isaacs and Fitzgerald 1999). For example:

> At this time we should question whether greater caution is required in interpreting the [WHI] results, or whether we should discard all information in the literature accumulated over the last 60 years based on one or two studies. . . . Irrefutable data should be collected and presented before adopting a negative attitude toward the use of estrogen in treatment of aging women. The WHI does not provide such a study. Since this publication hundreds of critiques have been published. The methodology, population involved, statistics, drug use, and the results have all come under question. . . . limiting [hormone therapy] to the treatment of climacteric symptoms only is unjustified. (Kopernik and Shoham 2004)

> The results of the WHI trial may be applicable to women who are remote from the menopausal transition. However, in the absence of an adequately powered study group in the menopausal transition it is not appropriate to define either clinical management of symptomatic 50- to 54-year-old women or to mandate discontinuation of appropriately initiated hormone therapy on the basis of the available data from the WHI. Estrogen's role in clinical cardioprotection remains an open question. All who can should continue to seek resolution of this critical personal and public health issue through the performance of appropriately timed and powered clinical trials. We hope that, in the interim, knowledge of the limitations of available RCTs will encourage caregivers, regulators, media personnel and women to consider or reconsider the issue of the potential cardioprotective effects of estrogen treatment during the climacteric. With many observational trials indicating a cardioprotective effect of early estrogen treatment and the absence of a prospective, randomized clinical trial powered to reveal cardioprotection starting during the menopausal transition it seems prudent not to dismiss such an effect. (Naftolin et al. 2004)

> *You can't practice medicine based only on randomized clinical trial data!* If we based our recommendations only on clinical trial data, we would never tell our patients who smoke to stop smoking. There is an enormous collection of biological and observational data indicating that hormone therapy given to apparently healthy women will reduce the risk of coronary heart disease. (Speroff 2002b, original italics)

Gynecologists were the first physicians to champion HT as a health-promoting agent, and it appears that they will be the last to give it up. Rather than accepting the fact that that estrogen does not benefit asymptomatic menopausal women, gynecologists appear to believe that the results of the WHI are wrong or, at best, that they should be promoting some other hormone preparation to healthy patients. A survey of 577 Belgian gynecologists (42% of all practicing gynecologists in Belgium), after WHI was discontinued, found that most continued to prescribe HT, although there was a shift away from the conjugated estrogen/medroxyprogesterone acetate preparation (Ena and Rozenberg 2003). Although other estrogens, progestins, or delivery systems might be superior, the WHI should have taught us not to trust promising theories or surrogate markers. There is no substitute for prospective randomized trials, and the supporters of other formulations should be required to perform such trials with disease endpoints prior to suggesting benefits.

THE CULTURE OF GYNECOLOGY

Medical specialties have discrete patterns of socially determined beliefs and behavior—in short, distinct cultures. Obstetrician-gynecologists primarily see healthy patients. This is unusual among medical specialties: pediatrics is the only other specialty in which most patients are free of chronic disease. Perhaps the dearth of real disease in their patient population predisposes gynecologists to expand their treatment offerings to include the promise of disease prevention, or even the prevention of aging.

Managing medications in healthy women gives a doctor something to do and ensures a continuing relationship with women no longer in need of obstetric expertise. The promise of eternal youth ensures the patients' consent and gratitude. Healthy women require little or no monitoring and are resilient enough to survive most prescriptions. One researcher suggests that: "Preventive use of HT had given gynaecologists a new important role in preventing diseases of old age, and possibly they did not want to lose it . . . In the case of HT, for example, gynaecologists benefited from new customers and a more respected position. In the Finnish context, prevention of major disease is considered more important than treatment of marginalized 'women's problems'" (Hemminki 2004).

Personality factors may contribute as well. Medical students who choose gynecology are often socially anxious, concerned about appearances and making a good impression, and emotionally vulnerable: "They see themselves as warm and helpful people, but at a deeper motivational level manifest a preference for experiences that make them feel potent and influential" (Zeldow and Daugherty 1991).

Reliance on expert opinion and personal experience rather than on evidence from randomized controlled trials may be common among physicians in general. A Canadian study surveyed attitudes towards evidence-based obstetric practice of 148 obstetric practitioners (including both family practitioners and obstetricians; Olatunbosun, Edouard, and Pierson 1998). When faced with a difficult clinical problem, 51% of these physicians consulted a respected authority, 37% consulted a textbook or clinical practice guideline, and only 8% used MEDLINE literature searches. Several physicians expressed concern about evidence-based medicine, fearing "erosion of physician autonomy" or stating that "evidence based medicine ignores clinical experience." The authors concluded that "personal experience and authoritarian views of experts still have an enormous influence in obstetric practice."

Reliance on experts is, in fact, reliance on the pharmaceutical companies that create and support these "experts" through research grants, consultancies, and speaker fees. Direct and indirect promotion of drugs, especially under the guise of impartial information, has been described as threatening rational prescribing (Collier and Iheanacho 2002).

The current culture of gynecology encourages the dissemination of health advice based on advertising rather than science. Randomized controlled trials have

proven that estrogens, alone or in combination with progestins, do not prevent cardiovascular disease in women and do not benefit health overall. It would be unfortunate if lower-dose preparations, transdermal delivery systems, and new combinations of hormones were accepted by gynecologists without relevant clinical trials. Gynecologists must switch allegiance from eminence-based to evidence-based medicine. Abandoning the quest for a hormonal fountain of youth in favor of recommending a healthful diet, increased exercise, and smoking cessation would truly benefit women's health.

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