Published in *Health Care for Women International*, Vol. 29, Issue 7, 2008, pp. 720-737.

Available online at http://www.tandfonline.com/doi/full/10.1080/07399330802179122

Update on Hormones, Menopause, and Heart Disease: Evaluating Professional Responses to the Women's Health Initiative

Paula S. Derry, Ph.D.

Paula Derry Enterprises in Health Psychology

Baltimore MD USA

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Address correspondence to: Paula S. Derry, Ph.D., 4811 Crowson Ave., Baltimore, MD, 21212, USA

E-mail address: paula.derry@gmail.com

Key words: Women's Health, Menopause, Hormone Therapy

Abstract

The Women's Health Initiative (WHI) randomized controlled clinical trials provided evidence that, contrary to the common wisdom and clinical practice of the day, estrogen and estrogen/progestin hormone therapies were not safe or effective interventions to prevent chronic illnesses, especially heart disease, among postmenopausal women. A recent criticism of WHI, the timing hypothesis, asserts that hormone therapies would be cardioprotective if started around the time of menopause. This article critiques the timing hypothesis. The hypothesis relies on rejecting traditional criteria for scientific evidence, overinterpreting weak evidence, underemphasizing harm, and valuing the metatheory that menopause is an estrogen deficiency disease.

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Introduction

Professionals disagree about whether postmenopausal hormone therapy (HT) is a safe and effective medicine to prevent chronic illnesses, especially heart disease, among midlife women. To understand how they arrive at different conclusions, it is important to consider how different professionals approach and assess research. In this paper, I continue my analyses of decision-making rules and values that help to clarify the varying judgments professionals make about what research shows and how to apply research to clinical practice (Derry, 2003, 2004). I discuss a recent development, the emergence of the "timing hypothesis," which asserts that if HT is started close to the time of menopause it will prevent heart disease and will be safe. The timing hypothesis has quickly become considered a plausible and important idea. Yet, as will be discussed, it relies on evidence that is at best weak and at worst muddled and inaccurate. Decision-making rules that support accepting the timing hypothesis include: not valuing rigorous scientific thinking (e.g., ignoring normal rules for judging what counts as scientific evidence, sometimes while claiming to be scientific); not placing a primary value on avoiding harm (e.g., considering heart disease outcomes while not simultaneously considering other risks such as stroke); and basing judgments on a preconception about menopause (i.e., that menopause is an estrogen deficiency disease that causes health problems). The timing hypothesis leads to believing that it is important to continue research on hormone use, less caution about prescribing hormones, broadening

indications for hormone use, and a re-affirmation of the idea that menopause is an estrogen deficiency disease.

Postmenopausal hormone therapy is an important issue in the United States and internationally. I examine the U.S. literature because this is my area of expertise. However, the U.S. literature is given great weight internationally. For example, after U.S. researchers discontinued their Women's Health Initiative clinical trial, British researchers discontinued their HT trial, the WISDOM study (Vickers, et al, 2007), the German Commission on the Safety of Medicines recommended drastically reducing prescriptions for hormones (Burgermeister, 2003), and prescription rates for hormones decreased all over the world. In addition, the decision-making rules that I identify are important to consider when examining the literature of any country.

Background

Beginning in the 1980s, professionals asserted that HT was a safe and effective medicine to prevent chronic illnesses, especially coronary heart disease (CHD) in postmenopausal women. This led to a large increase in HT prescriptions—in the United States, prescriptions increased from 58 million in 1995 to 90 million in 1999 (Hersh, Stefanick, & Stafford, 2004). Clinical trial evidence of a medication's safety and effectiveness, the "gold standard" for demonstrating cause-and-effect, is required for U.S. Food and Drug Administration (FDA) approval. Clinical trial evidence with regard to HT and CHD prevention did not exist. However, the great majority of over 40 epidemiological studies reported a 30% to 50% lower incidence in CHD for HT users compared with nonusers (see review by Barrett-Connor & Grady, 1998), and results were found for both primary and secondary prevention (Grodstein, Manson, & Stampfer,

1998). Many physiological mechanisms existed that could plausibly explain such a benefit (Herrington, 1997). HT had risks as well as benefits, most notably the possibility that breast cancer risk increased. However, since CHD is the most common cause of death among older women, when a CHD benefit was assumed in cost/benefit analyses an overall benefit for the majority of women was found (e.g., Col et al., 1997). The majority of professionals concluded that as a practical matter enough evidence existed to warrant recommending medication.

It is not uncommon in the U.S. for professionals to use medications for an "off label" use, based on their clinical judgments that the medications will be helpful even though not FDA approved for this purpose. In the case of HT for prevention, however, this was aggressively promoted. Beginning in the 1990s, professional guidelines increasingly recommended offering HT to all postmenopausal women for disease prevention. For example, the National Committee for Quality Assurance (NCQA, 2001), which creates standards of care, recommended that all women be counseled on HT use, and created a questionnaire to evaluate whether health plans offered this service.

It was common during this time period to assert that hormone "replacement" was necessary for the health and well-being of postmenopausal women because menopause is a state of estrogen deficiency (see discussion in Voda, 1997). Although postmenopausal women do produce estrogen in their bodies, these lower levels of hormone were assumed to be negligible. Women were said to live in a state of estrogen deficiency for the rest of their lives that triggered or worsened chronic illnesses ranging from heart to bone to brain disease. Further, this influence of menopause was thought to be the central fact determining health--although chronic illnesses have multiple causes, the idea was that

menopause did not simply contribute a small amount to these diseases; its impact was primary. With regard to coronary heart disease, for example, there was pessimism that lifestyle changes rather than hormones could impact significantly on CHD. This metatheory was expressed in the popular as well as the professional press. For example, *New York Times* health columnist Jane Brody (1997) wrote that "…Nature programmed [women] to live up to the age of menopause….A 50-year-old woman can expect to live another 35 years in a state of hormonal deficiency" and compared HT to insulin used by a diabetic. The idea that menopause is an endocrinopathy, powerful though it was, was not based on evidence, since little real information existed. Forty years ago menopause was "no more than a one-liner in a general textbook of gynecology" (Utian, 2003).

While this was the dominant position, during the 1980s and 1990s a minority of professionals disagreed and raised questions about using HT for prevention (for reviews see Barrett-Connor & Grady, 1998). For example, subject selection biases could account for the findings of the epidemiological studies since only a small minority of women used HT for long periods of time (Barrett-Connor & Steinke, 1999). The role of pharmaceutical companies in influencing opinion was discussed (Coney, 1994). Even before WHI, a literature was developing that questioned whether HT was a safe and effective way to prevent CHD (National Heart, Lung, and Blood Institute, 2002).

What Is the Women's Health Initiative?

The Women's Health Initiative (WHI) randomized controlled clinical trials put to the test the assertion that hormone therapies are safe and effective for preventing heart disease in postmenopausal women (Writing Group for the Women's Health Initiative Investigators, 2002; Women's Health Initiative Steering Committee, 2004). Twin

studies were designed in 1991-1992. Women who had a uterus received estrogen/progestin therapy (EPT) or a placebo. Women who had had a hysterectomy were randomized to receive either estrogen therapy (ET) or a placebo. The dependent variables were measures of actual heart disease—either myocardial infarction (MI, or heart attack) or death. Other major outcomes included breast cancer, then thought to be the major potential adverse outcome from HT, and, since HT has a variety of effects on a variety of body systems, a "global index" measured whether the overall effect of HT was helpful or harmful when a number of diseases were considered simultaneously. Secondary outcomes were also measured, including hip fracture, other fracture, other cardiovascular diseases, and certain cancers. Participants in the EPT trial were predominantly healthy women with an intact uterus aged 50-79; 8,506 women in the experimental group received hormone therapy (conjugated equine estrogens (CEE) 0.625 mg. and medroxyprogesterone acetate (MPA) 2.5 mg.), while 8,102 women served as controls. The ET trial included a total of 10,739 healthy hysterectomized women who received hormone therapy (CEE 0.625 mg.) or placebo. As originally designed, participants would be followed for 8.5 years. Both trials were ended prematurely because of ethical concerns that participants were being harmed. The EPT study was terminated in 2002 after 5.2 years because an excess number of EPT-users were developing breast cancer. The ET trial was terminated in 2004 because too many ET-users were having strokes.

The main result was that, contrary to expectation and the common wisdom of the day, HT did not prevent heart disease. Further, overall harm outweighed overall benefit in the global index. (For more detailed results see Chlebowski, et al., 2003; Hsia, et al.,

2006; Manson, et al. 2003; The Women's Health Initiative Steering Committee, 2004; Writing Group for the Women's Health Initiative Investigators, 2002.) WHI had weaknesses as well as strengths. For example, about half the participants had dropped out of the study by the time it ended, weakening the conclusions that could be drawn. However, the major conclusions of the study—that HT has no benefit for CHD risk and overall harm outweighed benefits—could reliably be drawn even given these limitations. The results implied that menopause is not an estrogen deficiency disease. For example, an FDA advisory stated that hormone medications should not be referred to as "hormone replacement therapy" [the common name at the time] since no evidence exists HT is a replacement of needed hormones (Federal Register, 2003).

Responses to WHI

The results of WHI were portrayed in the U.S. popular and professional press as a "bombshell" whose results were "met with puzzlement and disbelief by women and their doctors" (Kolata and Petersen, 2002), creating "confusion and upset" (Snyder, 2002). As previously discussed, professional opinion had in reality been mixed prior to these findings. However, WHI did have a significant impact on policy and practice. Many professionals were convinced by the WHI data, in combination with the emerging body of other experimental research, that EPT/ET is not effective for CHD prevention and that overall harm outweighs overall benefit for long-term disease prevention. Prescription rates fell (Hersh, Stefanick, & Stafford, 2004). The FDA concluded that HT should be used only for treatment of hot flashes, vaginal dryness, and possibly osteoporosis, at the lowest dose and for the shortest period of time (FDA, 2003). That is, while hormones should not be used for disease prevention, the level of harm was low enough to warrant

use for symptom control. Other professionals were not convinced by the WHI data, claiming that methodological flaws in WHI were so serious that conclusions could not be confidently drawn. For example, at a conference on the results of WHI (National Institutes of Health, 2002), a number of criticisms were raised, such as the use of only one EPT medication which, it was asserted, limited generalizability of results; participants who were not typical of hormone users; and other design flaws that left open the continuing possibility of primary prevention by CHD.

Timing Hypothesis

One criticism that arose immediately after the termination of the EPT study was that the WHI participants were not typical of hormone users, hence results did not generalize to the general public, because the WHI participants were "too old" (NIH, 2002). This speculation has been refined into a hypothesis, variously referred to as the "unified hypothesis" (Phillips and Langer, 2005), "timing hypothesis (Clarkson, 2007) and "early intervention" or "critical window hypothesis" (Harman, et al., 2005), that the effects of HT on coronary arteries vary critically depending upon how young or close to menopause a woman is when HT is started. In this view, no benefit was found in the WHI studies because the participants were too old, with an average age of 62, while most women begin HT right around the time of menopause for the purpose of treating distressing symptoms like hot flashes. A number of plausible biological mechanisms have been marshaled in support of the hypothesis. For example (Clarkson, 2007; Ouyang, Michos, & Karas, 2006), arteries may lose their ability to respond to estrogen (that is, receptor expression may be diminished) when women are older, so it is simply too late for estrogen to act beneficially. When older menopausal women use hormones,

they may already have subclinical or clinical coronary artery disease, and certain effects of estrogens may be harmful once disease already exists. For example, estrogens may cause plaques in artery walls to rupture, thereby causing clots, or clots may cause blockages only if arteries are already narrowed by disease. On the other hand, in a younger woman who does not have artery disease, estrogens may have beneficial effects such as preventing plaques from forming.

The timing hypothesis has quickly been regarded as very important in popular and professional articles. This emphasis suggests that the timing hypothesis is well proven by established facts or very plausible for other reasons. However, this is not the case. Let us first examine in more detail how the hypothesis has been taken up in the popular press and by professionals before examining the evidence.

The hypothesis has elicited great interest in the American popular and professional press. For example, a post hoc analysis of data (Hsia et al., 2006, discussed below) was reported in major American newspaper articles with titles like "Hormone therapy reversal. New study finds estrogen can benefit heart at or around menopause (Baltimore Sun, February 14, 2006)." The same study also attracted attention in the professional press. For example, an editorial in *Climacteri*c was titled "The pendulum swings back; estrogen is now beneficial if started at the right time" (Sturdee and MacLennan, 2006). Many opinion pieces that criticize WHI and assert the plausibility of the timing hypothesis have been published in professional journals (e.g., Mikkola and Clarkson, 2006; Phillips and Langer, 2005).

Introduction and Discussion sections of scientific papers discuss the timing hypothesis as one of the important theories that might bear on or limit their results. For

example, a paper reported the results of the WISDOM clinical trial of harms and benefits of HT. The authors (Vickers, et al., 2007) report increased risk of cardiovascular and blood-clot-related problems among their sample of 50-69 year old women. However, the authors qualify their results by the possibility that "Research is needed to assess the long-term risks and benefits of starting hormone replacement therapy near the menopause, when the effect may be different (p. 1)" and that "Clinical and animal studies suggest that the effect of oestrogen on the cardiovascular system and possibly the brain may be very different and probably beneficial when used at or near the time of menopause (p. 10)." Two research projects have been funded, the Kronos Early Estrogen Prevention Study (KEEPS, Harman, et al., 2005) and The Early versus Late Intervention Trial with Estradiol (ELITE, www.clinicaltrials.gov/show/NCT00114517) to provide clinical trial data pertaining to the plausibility of the hypothesis.

Professional groups issue guidelines, recommendations, and other writings that express the organizations' expert opinions and recommendations about what are good clinical practices. Guidelines are supposed to be evidence-based. The timing hypothesis has already been considered to be important enough to warrant mention in professional guidelines and opinions. The North American Menopause Society (NAMS) revised its recommendations for HT use in 2007. Following publication of the initial WHI results in 2002, NAMS (2003) had concluded that ET/EPT should not be used for primary or secondary prevention of CHD or stroke. The primary change in the updated position statement (NAMS, 2007) is to consider the timing hypothesis: "The role of ET/EPT in primary prevention of CHD remains unclear when considered for perimenopausal and early postmenopausal women if initiated early after reaching menopause and continued

for a number of years thereafter….Thus, ET/EPT use for primary prevention needs further evaluation." The American College of Obstetrics and Gynecology (ACOG, Press release, Sept. 30, 2004) reiterated that HT should not be used for disease prevention, but stated that "ACOG would like to see more research that answers key questions. Are the effects of hormones different for the most typical menopausal patient at the average age of 51…..Are hormones more dangerous or beneficial at one time of life than another, and, if so, why?" Guidelines provided by the American Association of Clinical Endocrinologists (AACE Menopause Guidelines Revision Task Force, 2006) similarly do not recommend HT for long-term disease prevention, but, again, state that "the major criticism of the results of the WHI trial is the age of the population of postmenopausal women who participated in the study….These women were more than a decade older than the age at which most women begin HT….The results of the WHI study cannot be generalized to a population of women in early menopause because the WHI was designed to evaluate HT in an older population of aging menopausal women." The International Menopause Society concluded (Press release, June 20, 2007): "Since most, if not all, women do not start hormone therapy at an old age, safety concerns on its possible adverse cardiac effects are actually invalid for the vast majority of hormone users. In fact, treatment seems to be associated with reduction of risk for coronary artery disease if initiated early."

It should be noted that not all professionals agree that the timing hypothesis is important or plausible. Most notably, the American Heart Association issued updated guidelines in 2007 for heart disease prevention in women that do not even discuss the timing hypothesis. The guidelines (Mosca, et al., 2007) emphasize lifetime heart disease

risk and the importance of all women engaging in prevention strategies. Their first line of intervention is altering modifiable factors, especially life style, before considering medications. About hormone therapy, the guidelines (p. 7) state that "Hormone therapy and selective estrogen-receptor modulators (SERMS) should not be used for the primary or secondary prevention of CVD," a recommendation that they classify as Class III (Not useful/effective and May be Harmful), Level A (Sufficient evidence from multiple randomized trials). A small number of other professional articles have been critical of the timing hypothesis (e.g., Grady and Barrett-Connor, 2007; Roberts, 2007), concluding that there is not enough scientific evidence to consider it important or well-established.

Evidence for Timing Hypothesis: WHI Subgroup Analyses

Clinical trial evidence directly testing the timing hypothesis does not exist. However, the WHI data itself has been analyzed for evidence bearing on the timing hypothesis, and in one case (Manson, et al., 2007, discussed below), an additional substudy was conducted with WHI participants. Professional guidelines and articles commonly cite these analyses as evidence that the timing hypothesis is plausible (e.g., American Association of Clinical Endocrinologists, 2008; NAMS, 2007). However, as will be discussed below, the analyses for the most part do not count as data by the normal rules of science.

Understanding the analyses requires looking closely at the technical details of the scientific methodology and results. There are rules by which scientists evaluate the soundness of research reports. Research outcomes count as data only if they are "statistically significant," which means they are unlikely to have occurred by chance but, instead, are a real result. Outcomes must have enough "power," another measure of

whether results are statistically reliable. If a study, for example, doesn't have enough participants, we can't be confident that the results are accurate. Outcomes for the main hypotheses are most important rather than after-the-fact, "post hoc" analyses. In part, this is because scientific results that are predicted before conducting a study are considered to be more reliable; researchers know that a few results will be statistically significant purely by chance when there are a large number of post hoc analyses. Further, any time researchers select some outcomes or variables to analyze or interpret while overlooking others, results are problematic. In clinical research, "primary" disease outcomes (for example, heart attacks) are more important than "secondary endpoints" (for example, coronary artery thickness) which may or may not end up causing problems. As will be discussed, WHI subgroup analyses violate many of these rules and provide little reliable data.

Hsia et al. (2006) found that hormone and placebo users in the ET study had equal numbers of actual coronary events (myocardial infarction or death). Similarly, there were no differences in heart problems between hormone and placebo users for younger women (aged 50-59). However, in a number of secondary, subgroup analyses, younger estrogen users had lower rates of coronary revascularization (HR 0.55 CI 0.35-0.86). Further, some composite measures (that added together the effects of a number of variables that all measured CHD problems) also gave results that were statistically significant. For example, among the 50-59 year olds, composite measures that included MI were statistically significant even though when MI was considered alone it was not. However, two of four composite measures were significant but two were not. The authors themselves point out (p.362) their analyses were underpowered. According to the

authors, 17,251 participants would be required for an adequately powered study, and they had 3,310, so that the results were statistically unreliable. Finally, there were no analyses that considered harm as well as benefit. An earlier article (Women's Health Initiative Steering Committee, 2004) had found significant elevations in stroke and deep vein thrombosis among ET users, but Hsia et al. did not consider these outcomes. The earlier study, but not the Hsia et al. study, looked at composite measures that included blood vessel problems (like blood clots) outside the coronary artery system (in addition to problems in heart blood vessels), and found overall harm in total cardiovascular disease when such events were included.

In conclusion, Hsai et al. reported only a "suggestion"--younger women may [or may not] benefit from HT. The results were not hard data. The significant results were for post hoc, secondary variables, not the primary variables of the study. Further, the results were for analyses that were statistically unreliable, selectively chosen, and the study did not include important information about harm that would affect one's judgment of overall safety or benefit. The authors of the WHI paper concluded: "[HT] provided no overall coronary protection in women who had undergone prior hysterectomy, although there was a *suggestion* [my italics] of lower CHD risk with [estrogen] in women 50 to 59 years of age (p. 360)." Yet, as stated above, popular and professional press reports called this study a "hormone therapy reversal." The NAMS 2007 updated professional guidelines state, without systematically evaluating the overall study: "[T]here was a statistically significant reduction in the composite endpoint of myocardial infarction, coronary artery revascularization, and coronary death in women aged 50 to 59 years randomized to E (NAMS, 2007)."

In another subgroup analysis (Rossouw, et al., 2007), results from the ET and EPT studies were combined to increase the number of participants, hence statistical power, in order to examine whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause. Again, their study has been taken to indicate support for the timing hypothesis. Again, their data are not reliable as conventionally defined by scientists: "Although not statistically significant, these secondary analyses suggest that the effect of hormones on CHD may be modified by years since menopause….Coronary heart disease tended to be nonsignificantly reduced by hormone therapy in younger women or women with less than 10 years since menopause….(p. 1471)" Grady and Barrett-Connor (2007) point out 137 statistical tests were performed, so that finding a few that were statistically significant was less convincing. Even though the outcomes were not statistically significant, the authors conclude (pp. 1471-72) "Our findings are consistent with findings from observational studies of the association of years since menopause with carotid intima-media thickness….Estrogen may have dual and opposing actions, retarding the earlier stages of atherosclerosis through beneficial effects on endothelial function and blood lipids, but triggering acute events in the presence of advanced lesions through procoagulant andinflammatory mechanisms." Thus, here again we have statistically unreliable data, overgeneralized (even if the results supported the timing hypothesis it is a big leap to say that they support specific biological mechanisms). In addition, there were data indicating harm: risk of stroke was elevated regardless of years since menopause.

Manson and colleagues (Manson et al., 2007) conducted a substudy of WHI ET participants. Computed tomography (CT) images of the heart, taken on average 7.5 years

after randomization, were obtained for 1064 women who had been 50-59 when the study began. Coronary-artery calcium scores taken from the CT images, which indicate plaque development and therefore future CHD risk, were lower in ET users The authors conclude (p. 2599) that "estrogen therapy initiated in women at 50-59 years of age is related to a reduced plaque burden in the coronary arteries and a reduced prevalence of subclinical coronary artery disease, providing support for the hypothesis that estrogen therapy may have cardioprotective effects in younger women….Conclusive answers, however, can be derived only from large-scale trials involving sufficient numbers of clinical events among women in early menopause."

This study provides information about a secondary marker, encouraging future research, but is not in itself data about heart disease. Further, the authors argue that results apply to women in "early menopause." However, an unknown but significant percentage of the ET participants were not newly menopausal when the study began. A nonhysterectomized woman would likely be newly menopausal in her early fifties, but these were hysterectomized women. It is difficult to determine when a hysterectomized woman without oophorectomy actually reaches menopause. Using the authors' criteria for estimating this, the mean age at menopause was 43.8 vs. 43.4 years for the hormones and placebo groups, respectively. If we look at participants' ages when the study began, and the average numbers in each group who had oophorectomies (so we know they were menopausal) when hysterectomized, we also know that a significant percentage, at a minimum, of women were not newly menopausal at recruitment. Participants 50-59 years old were therefore on average 6-15 years postmenopause when the study began, not "newly menopausal," and yet, according to the authors, were benefiting from HT.

Further, the assertion is made that results pertain to "postmenopausal women." However, hysterectomized and naturally menopausal women (who were not participants in the ET study and therefore not in the CT study) differ in both known and unknown ways that might affect results. For example, naturally menopausal women do produce some estrogen and often have different health histories from hysterectomized women.

Evidence for Timing Hypothesis: Animal studies, epidemiological studies, and biologically plausible mechanisms

Animal studies, epidemiological studies, and biologically plausible mechanisms have also been cited as evidence that the timing hypothesis is plausible in professional articles and in opinion statements by professional groups (e.g., American Association of Clinical Endocrinologists, 2008; Harman et al., 2004).

A variety of mammals have been studied (see Ouyang, Michos, and Karns, 2007) but the most cited animal studies are those of Clarkson and his colleagues on cynomolgus monkeys (e.g., see Clarkson, 2007). Clarkson's studies show that oophorectomized animals have lower rates of coronary artery problems if provided with replacement hormones, but only if medication is provided soon after surgical menopause. In a recent paper, Clarkson (2007) argues that his research supports the timing hypothesis. Further, he asserts that estrogens are the key to cardiovascular health. However, while he does not consider lifestyle to be of central importance, his monkeys develop heart disease only when fed a high-fat, atherosclerotic diet (Clarkson, 1998), and it is high-stress (i.e., low status) monkeys who are most vulnerable to disease. Surgical and natural menopause are assumed to be equivalent. Menopause is a universal in the human life course but not for monkeys, and his monkeys were young not middle-aged when oophorectotmized. The

assumption is made that HT is a replacement rather than a drug. Finally, his review of possible biological mechanisms ignores negative effects of estrogens such as stroke and deep vein thrombosis.

In epidemiological studies hormone users had fewer heart problems, while in experimental studies they did not. Proponents of the timing hypothesis argue that this is because epidemiology studies look at women who are more typical hormone users, newly menopausal women with symptoms like hot flashes (Grodstein, Manson & Stampfer, 2006; Harman et al., 2004). Epidemiological studies have recently been reanalyzed to show that it was younger women in these studies who benefited from hormones (e.g., Grodstein, Manson, & Stampfer, 2006; Salpeter, Walsh, Greyber, & Salpeter, 2006). As stated above, a number of biological mechanisms have been offered that would plausibly account for why younger women benefit from hormones while older women do not. Epidemiological studies and biological mechanisms thus make a case that the timing hypothesis is plausible. However prior to WHI these same sources of data were interpreted to mean that hormones were cardioprotective for all women. Prior to WHI, the argument was not widely made that these sources of evidence suggested a timing effect; this argument arose only after the WHI data were collected. Further, WHI is criticized for participants who are not typical, but the same criticism is not applied to epidemiological studies--only a small minority of women use hormones for long periods of time and they are more likely to have had surgical menopause.

Research inconsistent with the timing hypothesis

There are also observational studies inconsistent with the timing hypothesis or indicating harm from using HT. These studies are typically not cited in professional guidelines and other publications that support the timing hypothesis.

Weiner and colleagues (Weiner et al., 2007) used the same criteria to select participants as the WHI researchers. Using clinic records, and with a large enough number of participants to have statistical power, these researchers found that among women aged 50-54, hormone use had no effect on heart attack, but hormone users had higher rates of stroke, blood clots, and breast cancer. A series of studies (Glass, Lacey, Carreon, and Hoover, 2007; Ravkin et al., 2007) found that breast cancer rates dropped for estrogen-positive cancers among postmenopausal-aged women in the years following WHI, coinciding with the time period that HT use had declined.

Discussion

The Women's Health Initiative clinical trials provided strong clinical trial evidence that postmenopausal hormone therapy does not prevent heart problems. Further, overall harm outweighed benefits when a number of illnesses were considered simultaneously. The timing hypothesis asserts that this finding pertains only when women begin hormone use many years after menopause or when they are old. Supporters of the timing hypothesis cite animal studies, epidemiological studies, plausible biological mechanisms, and subanalyses of WHI data. However, as discussed, all of this evidence is weak at best.

How do professionals assess whether or not the timing hypothesis warrants serious consideration? Do they conclude that the WHI results pertain to all of the participants in the study, since the timing hypothesis is, as of yet, a weakly supported

speculation? Or do they conclude that WHI results can confidently be applied only to older women because a plausible criticism exists? When does a possibility require serious consideration, and when is it not taken into account until it is better validated? What decision-making rules or values help to clarify the judgments of different professionals?

One important decision-making heuristic is whether credence is given to traditional rules for evaluating scientific evidence. According to standard rules, clinical trial data count as strong evidence. Interpretation of clinical trial data is most reliable when hypotheses are predicted beforehand rather than analyzed post hoc, when variables measure diseases rather than predictors of disease, and when studies are methodologically sound in other ways. Statistical significance and statistical power provide measures of whether results are real or random fluctuations. One area of special contention has been what conclusions can be drawn from epidemiological studies. The updated American Heart Association guidelines (Mosca, et al., 2007) and professional articles critical of the timing hypothesis (Grady and Barrett-Connor, 2007; Roberts, 2007) rely heavily on traditional scientific criteria. Guidelines and other professional opinions which give great credence to the timing hypothesis (e.g., NAMS, 2007) rely on weaker evidence that does not count as scientific data, such as results which are not statistically significant but which appear suggestive, and give great credence to a plausible case based on epidemiological studies and plausible biological mechanisms.

Ironically, WHI demonstrated that weaker forms of evidence, no matter how fervently believed or plausible, did not accurately describe the real cause-and-effect situation. Prior to WHI it was believed that hormone therapy was effective at preventing

heart problems for all postmenopausal women. Professional guidelines did not typically state that a window of opportunity existed in which healthy younger postmenopausal women benefit while others would would not. Indeed, guidelines often suggested that a woman's risk of heart disease be used to help her to decide whether to use HT-- in other words, a woman at high risk of heart disease would be more likely to benefit overall from HT. Wyeth, the manufacturer of the best-selling ET/EPT medications Premarin and Provera, requested, based on the weaker evidence, that the FDA approve HT for heart disease prevention without requiring clinical trial evidence. After the FDA refused, Wyeth funded a secondary prevention trial, the HERS trial, expecting to demonstrate that women with established heart disease would have fewer recurrences of heart problems if treated with ET/EPT. Like the WHI, HERS found no benefit to HT.

Why might professionals not give scientific reasoning a primary value? In clinical practice, weaker evidence is relied on and useful when an issue is important and stronger evidence does not exist. Clinicians who must make decisions about action in the real world often must rely on weaker forms of evidence. For example, epidemiological studies can be useful guides to action and are often thought of in terms of cause-and-effect in such a situation (Mosca, 2001). Professionals may also value and draw on other sources of knowledge, such as clinical judgment, opinions of authorities, and personal experience. What, however, is important about HT use for CHD prevention?

It is sometimes asserted that establishing the safety of HT is important to reassure women who have been prescribed the medication to treat menopausal symptoms. However, the primary risks identified in the WHI studies are not heart disease; they are strokes, blood clotting problems, and breast cancer. Further, Grady and Barrett-Connor

(2007) suggest that the risks for symptomatic women using HT for limited periods of time (as opposed to large numbers of women using HT for extended periods of time for prevention) are acceptably low.

Heart disease is the most common cause of death in older women. Finding prevention methods that work is therefore of great importance. It might therefore be important to know whether HT provides safe and effective prevention if begun soon after menopause and continued for a number of years. However, we cannot know this. Scientific evidence does not currently exist. The currently funded KEEPS and ELITE research studies are looking at secondary measures, not actual disease outcomes. A clinical trial of younger postmenopausal women who use hormones for many years is unlikely, given the large numbers of participants needed, cost, etc. Even if it were found that younger women had a CHD benefit, it is possible that as they age and their risk factors accumulate, that HT would not continue to have a benefit. Thus, ET/EPT for prevention can only be based, at least for the foreseeable future, on weak, uncertain data, and not on the clinical trial data that is normally required to prove safety and effectiveness. Further, since evidence suggests that HT has significant risks, it would be especially important to evaluate its safety before prescribing it for prevention.

Even if it could be proved that HT, if started early and continued for many years, lowered heart disease risk, HT would still not be a good medication to use for this purpose. Since the argument is that medication must begin while women are healthy and close to menopause, the number needed to treat—that is, the number of women prescribed medication in order for one woman to benefit—would be very high. With large numbers of women using medication for long periods of time, adverse events, even

if rare, would add up to large numbers of women. Breast cancer, strokes, blood clots outside the coronary artery system, are all risks associated with HT use. Indeed, continued research about long-term use of hormones itself has the potential to harm participants, as has already happened in WHI, HERS, and other clinical trials. Further, lifestyle interventions and other medications, including those that are effective at later stages of CHD, already exist.

How can we understand professionals who believe that the timing hypothesis is important? Many factors, ranging from vested interests to a sincere desire to be helpful, might all play a role. The possible influence of pharmaceutical companies in creating a research agenda that would increase HT use cannot be ignored. An additional decision-making rule is that professionals advocating the timing hypothesis appear to endorse the metatheory that menopause is a state of estrogen deprivation that creates or exacerbates disease. Only this assumption makes it sensible to believe that estrogen replacement started near the time of menopause will have a crucial and unique impact on heart disease risk. It is consistent with this assumption that results for women with natural and surgical menopause, monkeys and humans, are all considered equivalent. It is understandable that if a metatheory is believed, weak data will appear inherently plausible.

Conclusion

It is likely that professionals will continue to differ in their evaluation of hormone therapies for postmenopausal women. In order to make sense of why professionals arrive at differing opinions, it is useful to look at their decision-making rules and values. For the timing hypothesis, important heuristics include whether or not a professional gives credence to conventional rules by which scientific studies are evaluated, whether or not

the professional has a preconceived idea that menopause is a deficiency disease causing health problems, and how the professional factors the possibility of harm into his or her judgments. The reality is that professional reports and the opinions of experts, even those of respected professionals, may be of questionable quality.

The bottom line for judging women's health research and recommendations is that they are held to rigorous scientific standards, that they report on harmful as well as helpful results, that they properly caution interpretation of weaker studies, and that they reject the hypothesis that menopause is a disease. Even when professionals have differing opinions, women's health advocates and scientists should hold them to accepted standards for health research.

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