New evidence rekindles the hormone therapy debate

Noreen Goldman

Background
In a now well-publicised series of events during 2002 and 2003, the Women’s Health Initiative (WHI) and other randomised controlled trials (RCTs) designed to examine the links between postmenopausal hormone therapy (HT) and the prevention of chronic disease were terminated prematurely. The estrogen plus progestin arm of the WHI was terminated when a global health index indicated overall harm and a significantly higher breast cancer risk for the treatment group, and the estrogen arm was stopped because of an increased risk of stroke in the absence of evidence of cardioprotection.

Expectations that HT would be beneficial for the prevention of heart disease were not borne out by the RCT results. In contrast to most observational studies that reported lower rates of coronary heart disease (CHD) for long-term users of HT, RCTs suggested no reduction or an increased incidence. In particular, estimates of the relative risk of CHD associated with HT use from the estrogen arm of the WHI suggested no cardiovascular benefit, whereas those from the estrogen plus progestin trial indicated excess risks of a magnitude of 1.2 to 1.3. These conflicting findings generated a huge response from the public, researchers and clinicians.

Recent evidence regarding the sources of discrepancy between the observational studies and the RCTs provides us with a timely opportunity for a fresh perspective on the HT controversy. These analyses, which have received far less publicity than the initial WHI findings, oblige us to both examine the implications for the exalted status of RCTs triumphed. Epidemiologists assessing the discrepancies between the two types of studies generally implicate biases or confounders in the observational data. Some considered the HT controversy to be a debacle for epidemiological research and others went so far as to predict the demise of observational studies. Nevertheless, some researchers levelled criticisms against the RCTs, pointing out, for example, that differential rates of unblinding between treatment and control groups, high discontinuation and crossover rates, and a relatively old age distribution of participants in the trials – discussed in further detail later – could have biased estimates from the RCTs.

The HT controversy and its consequences
In the presence of divergent findings between many well-conducted observational studies, such as the Nurses’ Health Study (NHS), and a small number of high quality RCTs, the RCTs triumphed. Epidemiologists assessing the discrepancies between the two types of studies generally implicated biases or confounders in the observational data. Some considered the HT controversy to be a debacle for epidemiological research and others went so far as to predict the demise of observational studies. Nevertheless, some researchers levelled criticisms against the RCTs, pointing out, for example, that differential rates of unblinding between treatment and control groups, high discontinuation and crossover rates, and a relatively old age distribution of participants in the trials – discussed in further detail later – could have biased estimates from the RCTs.

The consequences of the WHI findings went far beyond academic debate. The prevalence of HT plummeted in the USA and in other countries beginning in 2002; clinical guidelines were modified to advise against the use of HT for prevention of cardiovascular disease; and postmenopausal women and their physicians were confronted with difficult decisions about hormonal use. Women with unpleasant or debilitating menopausal symptoms frequently abandoned HT and many continue their struggle to find satisfactory alternatives.

Resolving the discrepancies
Various studies suggest that the discrepancies between observational studies and RCTs may be due in large part to differences in the timing of HT initiation relative to the onset of menopause. Women taking hormones in observational studies had typically begun therapy in early menopause, whereas participants in the major RCTs had been assigned treatment more than a decade after menopause, on average. Several types of evidence supporting the importance of a woman’s age or duration since menopause at the initiation of HT have now emerged: (1) a secondary analysis based on pooled data from the two WHI trials yielded a significant trend in relative risk for CHD, with women at higher durations since menopause onset experiencing higher relative risks than those adopting HT closer to menopause onset; (2) re-analysis of the NHS showed a similar pattern; (3) stratification of WHI and NHS estimates of CHD risk by timing of HT initiation eliminated much of the difference between the two sets of results; and (4) a meta-analysis based on 23 RCTs indicated lower CHD risk among HT users than non-users only for studies comprising relatively young postmenopausal women or women within a decade of menopause onset. Although not all trends were statistically significant, estimates of relative risk for incidence of coronary disease and total mortality derived from these studies (Table 1) show a consistent pattern by age or time since menopause: protective effects at early ages or durations of HT use and progressively higher relative risks in later years. Additional evidence comes from the WHI Coronary Artery Calcium Study (WHICACS), which was initiated in 2004 among 50–59-year-old women in the estrogen-only arm of WHI: estrogen users had lower levels of calcified plaque (a marker of total atherosclerotic plaque burden) in their coronary arteries compared with the placebo group.

The evidence for age modification of HT effects is strengthened by its biological plausibility. Clinical trials in women and experiments involving non-human primates suggest that exogenous estrogen has complex, counteracting effects on coronary function that vary with the stage of atherosclerosis: at early stages, estrogen may lower coronary risk by improving lipid and endothelial function, but the prothrombotic and pro-inflammatory effects of estrogen may result in clotting or rupture of plaque at more advanced stages. Thus, a woman’s age and time since menopause at HT initiation are likely to be surrogate variables for the degree of vascular disease.

Limitations of RCTs
These new findings underscore some of the well-known limitations of RCTs. Despite serving as the gold standard of...
clinical research, their lack of external validity continues to be a serious concern. The sample participating in clinical research, their lack of external validity continues to be a serious concern. The sample participating in clinical trials is rarely a random sample from a well-defined population or representative of the population of interest. Although cost and sample size considerations, along with clinical interest in prescribing HT for disease prevention in older women, led WHI investigators to implement a broad age range (50–79 years), the vast majority of women outside of clinical trials adopt HT within several years of menopause.\(^3\) For example, 80% of hormone users in the Women’s Health Initiative.

### Table 1

<table>
<thead>
<tr>
<th>Study data</th>
<th>Age (years)</th>
<th>Years since menopause (n)</th>
<th>Hazard ratio for CHD (95% CI)</th>
<th>Hazard ratio for total mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50–59</td>
<td>60–69</td>
<td>70–79</td>
<td>p value for trend(^a)</td>
</tr>
<tr>
<td>Women’s Health Initiative (WHI)(^2)</td>
<td>Estrogen + progestin</td>
<td>1.29</td>
<td>1.03</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>Estrogen alone</td>
<td>0.63</td>
<td>0.94</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>Combined HT</td>
<td>0.93</td>
<td>0.98</td>
<td>1.26</td>
</tr>
<tr>
<td>Nurses’ Health Study(^b) (NHS)(^2)</td>
<td>Estrogen + progestin</td>
<td>0.86</td>
<td>1.15</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Estrogen + progestin (adherence adjusted)</td>
<td>0.78</td>
<td>1.36</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis(^c) (23 RCTs)(^3)</td>
<td>0.68</td>
<td>1.03</td>
<td>–</td>
</tr>
<tr>
<td>WHI (combined HT)(^2)</td>
<td>0.70</td>
<td>1.05</td>
<td>1.14</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis(^c) (30 RCTs)(^3)</td>
<td>0.61</td>
<td>1.03</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^a\)The p values for trend for the WHI are based on parameterisations of age as a linear form of categorical coded values. The p values for the NHS are tests for interactions.

\(^b\)Based on viewing the NHS as a randomised trial, using intention-to-treat analysis. Adjusted for baseline variables. The second set of estimates excludes women with past use of HT and is adjusted for adherence.

\(^c\)In the meta-analysis for CHD, RCTs are classified in the two following groups: (1) mean age of participants <60 years or mean years from menopause <10 years; (2) mean age of participants >60 years or mean years from menopause >10 years. In the meta-analysis for total mortality, the two groups are defined as (1) mean age <60 years and (2) mean age >60 years. Estimates from the meta-analyses are odds ratios.

CHD, coronary heart disease; CI, confidence interval; HT, hormone therapy; NHS, Nurses’ Health Study; RCT, randomised controlled trial; WHI, Women’s Health Initiative.
market.37,38 In contrast, the major external validity problem for RCTs of HT is under-representation of relatively young (postmenopausal) women rather than the elderly.

Although recent analyses of discrepancies between the RCTs and observational studies have focused much of their attention on disparities in the underlying ages and durations since menopause of study participants, additional WHI limitations may have given rise to the conflicting findings. For example, the much higher proportions of women unblinded in the estrogen–progestin arm of the WHI (primarily because of vaginal bleeding) as compared with the placebo group (0.44 vs 0.07) made the trial resemble an observational study.11 Detection bias resulting from this differential awareness of HT status between treatment and control participants may have led to overestimates of the differential awareness of HT status between treatment and control. Moreover, without comparative studies derived from both observational and experimental data, it would have been challenging to identify how the health risks of HT vary by timing and duration. High-quality observational studies may now be our best hope for gaining additional insights into the biological mechanisms underlying the apparent changes in the effects of HT over a postmenopausal women’s life course.

Acknowledgements

The author would like to thank Ronald Brookmeyer, Diana Glei, Graham Lord and James Trussell for their helpful advice and Diana Sacké for assistance with the manuscript.

Statements on funding and competing interests

Funding Partial support came from the Demography and Epidemiology Unit of the Behavioral and Social Research Program of the National Institute on Aging (R01AG16790) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R24HD047879).

Competing interests None identified.

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BOOK REVIEW


This book has been published on behalf of the College of William and Mary and the Colonial Williamsburg Foundation in the USA, both of which coincidentally I came across this summer while in Virginia. It is very clear that Americans have a deep relationship with their colonial heritage and take huge pride in authenticating and recreating their origins, as anyone who has visited Williamsburg can attest. Similarly, this book has been meticulously researched from a wealth of sources and challenges old assumptions on fertility and family planning in colonial times. The author’s central theory is that American women began to reject the legitimate use of childhood and started to limit births more than 100 years in advance of Western Europe, with the exception of France; an alternative ‘American revolution’ that was invented and implemented by women themselves.

This book is not easy bedtime reading material and has numerous footnotes with historical references. It relates to many diverse ethnic, cultural and religious groups such as the Quakers, the Pennsylvania Dutch, rural and urban populations. There are attractive illustrations of women and family groups, often portrayed with fruit and flowers as iconic props representing ‘female promise and procreation’. There is a complex association throughout with the demographics of enslaved women; I would have liked a chapter specifically on the impact of race and patterns of childbirth. Thomas Jefferson, the third USA president, took up with a slave, Sally Hemmings, after the death of his wife in 1782. Modern DNA testing has suggested his lineage continues in the current African-American population although, as a consummate politician, he denied any carnal relationship with a slave at the time.

The birth control chapter states that most historians conclude that contraception was not significant in colonial America. The author disputes this and found examples to the contrary, but mainly referencing herbal remedies from diaries, physicians and doctors’ notes. She found little reference to sexual abstinence other than with nursing mothers. Given the lack of effective contraception from the modern perspective, it is not exactly clear what underpins the revolutionary limitation of family size.

In summary, if you are writing a PhD on historical patterns of fertility in North America this book will be a godsend. For the rest of us, it may provide a little dustyness on the bookshelf but was an interesting read over the Christmas break nonetheless.

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