EDITORIAL COMMENTS

Randomised trials on the long-term effects of hormone replacement therapy: Criticism of Women's Health Initiative Study

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Use of hormone replacement therapy (HRT) has increased among postmenopausal women in western countries: an estimated 20 million women worldwide were using HRT in the late 1990s[1]. Approximately 38% of postmenopausal women in the United States use hormone replacement therapy[2]. In 2000, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States and accounting for more than $1 billion in sales, and 22.3 million prescriptions were written for Prempro (conjugated estrogens plus medroxyprogesterone acetate) [3].

Prempro is currently FDA-approved for: 1) treatment of moderate-to-severe vasomotor symptoms associated with the menopause, 2) treatment of vulvar and vaginal atrophy, and 3) prevention of postmenopausal osteoporosis. Early evidence from studies of unopposed estrogen suggested that it lowered risk of cardiovascular disease, consistent with results from studies of intermediate markers that showed beneficial changes[4]. However, recent evidence from secondary prevention trials and observational studies using combined estrogen/progestin therapy showed increased risk of coronary heart disease (CHD) in the first year[5-7]. This may reflect prothrombotic and proinflammatory effects of progestins that outweigh any effects of estrogens on atherogenesis and vasodilatation.
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Randomised trials on the long-term effects of hormone replacement therapy

The long-term effects of HRT on cancer and cardiovascular disease have been debated since HRT was first prescribed, and various randomized trials were designed to provide reliable unbiased information on the incidence of these outcomes[5,8-16]. Four of these trials[5,8-10], two of which ended prematurely[8,9], have published their main results (the Women's Health Initiative (WHI) [8,15] published results for part of the trial only).

The four trials with published results included over 20000 postmenopausal women, followed for 4.9 years, on average. The active treatment was combined oestrogen/progestagen in three trials[5,8,9] and oestrogen-alone in one: Women's Estrogen for Stroke Trial (WEST).[10] Three trials recruited women with previous cardiovascular disease and WHI recruited healthy women.

There was no significant heterogeneity in any of these results across the trials, suggesting that the relative risks associated with the use of HRT do not vary substantially across women with different underlying risks of cardiovascular disease or using different hormonal preparations.

The finding for seven, potentially fatal, conditions that were primary or secondary outcomes were: cancer of the breast, endometrium, and colorectum; CHD; stroke; pulmonary embolism; and fractured neck of femur (Table 1). Overall, for women randomised to HRT compared with placebo, there was: a significant excess of breast cancer (relative risk 1.27), stroke (1.27), and pulmonary embolism (2.16); a significant deficit of colorectal cancer (0.64) and fractured neck of femur (0.72); but no overall significant excess or deficit for endometrial cancer (0.76) or CHD (1.11).

Results from randomised trials broadly agree with

findings from observational studies for cancer of the breast and colorectum[1,17], and also for pulmonary embolism[18] and fractured neck of femur[19]. Moreover, the WHI reported an increasing risk of breast cancer over time[8], corresponding to the increasing risk of breast cancer with duration of use of HRT found in observational studies[15]. Both trial and observational data showed that the risk of venous thromboembolism was greater soon after starting HRT than in later years[5,8,18]. Since objective trial data have confirmed previous observations for these conditions, we can conclude that the findings are true effects of HRT, and not due to bias or confounding.

By contrast, the results from many observational studies, suggesting that both combined oestrogen/progestagen and oestrogen-alone HRT substantially reduce the risk of CHD, must now be regarded as severely biased. Many commentators had argued that the lower rates of CHD among HRT users compared with non-users found in observational studies did not necessarily mean that HRT protected against the disease (Table 1)[1,15,18]. It was the need for unbiased data on the incidence of CHD that prompted the setting up of most of the randomised trials. Unexpectedly, results from Heart and Estrogen/Progestin Replacement Study (HERS) suggested an adverse effect of HRT on coronary disease in the first year after randomisation[5,16] and findings from WHI were in a similar direction, but not significant[8]. Nevertheless, neither trial has shown long-term benefit for coronary disease[5,8,16]. Given the consistent evidence from all trials of little or no benefit, previous claims that HRT substantially protects against CHD should now be discounted. The increased incidence of stroke among HRT users in the randomised trials is a new finding. Results from observational studies were mixed[18] but now that there is consistent trial evidence of an increase for all strokes combined, the effect of HRT on subtypes of stroke warrants further investigation.

No trial was designed with all-cause mortality as an endpoint, as it is an insensitive marker of any specific effect of HRT. The fact that the trials found no change in all-cause mortality (relative risk 1.03, for all trials combined) merely means that HRT does not have an immediate, substantial, and non-specific effect on mortality. Unfortunately, the trials are too small to provide much-needed reliable evidence about the effects of long-term HRT on cause-specific mortality (Table 1).

Table 1. Summary of results for seven major conditions in trials of HRT

HRT/placebo	Events (n)	Relative Risk
Breast cancer (HERS, WEST, WHI)	205/154	1.27
Endometrial cancer (HERS, WHI)	24/30	0.76
Colorectal cancer (HERS, WHI)	56/83	0.64
Coronary heart disease (HERS, WEST, WHI)	357/316	1.11
Stroke (HERS, WEST, WHI)	272/208	1.27
Pulmonary embolus (HERS, EVTET, WEST, WHI)	86/38	2.16
Fractured neck of femur (HERS, WEST, WHI)	68/89	0.72

Women's Health Initiative Study

This study was designed to assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States. The WHI study is a randomized controlled primary prevention trial (planned duration 8.5 years) in which 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998. Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or placebo (n = 8102). The primary outcome was coronary heart disease (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the two primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs. placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. Another WHI study is assessing whether long-term use of an estrogen preparation (Premarin) in postmenopausal women who do not have a uterus, will decrease the risk of CHD in that population. This study is still ongoing. Until this study is completed, long-term use of estrogen products to prevent cardiovascular disease should be considered investigational.

WHI study concerning Prempro includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) were as follows: CHD, 1.29 with 286 cases; breast cancer, 1.26 with 290 cases; stroke, 1.41 with 212 cases; PE, 2.13 with 101 cases; colorectal cancer, 0.63 with 112 cases; endometrial cancer, 0.83 with 47 cases; hip fracture, 0.66 with 106 cases; and death due to other causes, 0.92 with 331 cases. Corresponding HRs for composite outcomes were 1.22 for total cardiovascular disease (arterial and venous disease), 1.03 for total cancer, 0.76 for combined fractures, 0.98 for total mortality, and 1.15 for the global index. Absolute excess risks per 10 000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

The results of the WHI study confirm what already is known about the long-term risk of HRT, including breast cancer and venous thromboembolism. HRT has not been proven to be beneficial in preventing CHD and in fact may result in a small increased rate of CHD.

Criticism of Women's Health Initiative Study

- During the study, 42% of women receiving active drug and 38% of those receiving placebo stopped taking their assigned medications and this invalidates the statistical data.
- The majority of HRT complications were not fatal.
- The mortality caused by cardiovascular accidents among the group undergoing placebo was 1.3 thousandth per year, while for the group undergoing the hormone treatment was 1.5 thousandth, a difference which is very minute: but since the objective was only to verify the effect on the cardiovascular system and once the answer was found it was decided to suspend the research.
- All women took estrogens and progestin through oral route of administration and not transdermal route (patches). The passage through the liver could alter the hormonal composition.
- The sample tested in this study was very old; 67% was over 60 years old, in spite the fact that the treatment should normally begin at the age of about 50, and 22% was over 70 years old. In this sort of sample the risk of cardiovascular diseases is very high.
- People at risk or people who previously had similar diseases should not take hormones. And that is not all:
  - 35% of the sample was hypertensive
  - 13% had high cholesterol level
  - 33% was overweight.
- In the USA, hormones are prescribed to everyone.

It is the rule and fashionable. In Europe, doctors are cautious. It is important to remember that menopause does not necessary require therapy. Not always and in anyway.

- The WHI study was not designed to look at the short-term risks and benefits of HRT for the relief of menopausal symptoms. It was designed purely to establish the long-term risks and benefits of HRT, particularly with respect to heart disease.
- The balance of risks and benefits of HRT for its licensed indications remains favourable. The American research did not take into consideration this fundamental aspect: many women are depressed, demotivated towards life (suicides considerably increase in menopause), and they have panic attacks, problems regarding work performance, in both partner and sexual relationships. HRT is mainly used for this, to give quality to the women's life: social, emotional or working. Presently medicine is going in this direction, towards an extension of youth and not of old age.

Comment

The results of the study caused an uproar in the media, health-care and social issues And of course, emotional, for those millions of women in menopause all over the world who undergo HRT and suddenly are told that the race for eternal youth is actually a leap in the dark.

How should clinicians and women taking HRT behave?

- Combination HRT is only indicated for the treatment of menopausal symptoms and prevention of osteoporosis, and not purely for long-term prevention for heart disease.
- Initiation of HRT should be based on review of the risks and benefits of treatment for the individual woman.
- Any immediate changes to women's treatment are not necessary.
- However, women on HRT should have their therapy and health regularly reviewed (especially with long-term use), and should be encouraged to have mammography and cervical screening as appropriate for their age.

Take home message

- The decision whether to begin or to continue therapy must be individualized, taking into account the known benefits and risks of therapy, as well as alternative treatment. As is true for all medications, the lowest effective dose should be sought.[20,21]
- If the woman feels that she benefits from using HRT and is concerned by these findings, there is no need to stop taking HRT immediately. However, she should discuss this information and her concerns with her doctor.

ΠΕΡΙΛΗΨΗ

***Δ. Πανίδης, Α. Κούρτης*. Τυχαιοποιημένες μελέτες μακροχρόνιας χορήγησης θεραπείας ορμονικής υποκατάστασης: κριτική της μελέτης Women's Health Initiative.**

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Η χρήση της ΘΟΥ στις μετεμμηνοπαυσιακές γυναίκες έχει αυξηθεί σημαντικά τα τελευταία χρόνια. Παγκοσμίως, είκοσι εκατομμύρια γυναίκες έπαιρναν ΘΟΥ στο τέλος της δεκαετίας του 90. Στις Η-ΠΑ, το 38% των μετεμμηνοπαυσιακών γυναικών λαμβάνει ΘΟΥ. Το 2000, 46 εκατομμύρια συνταγές γράφηκαν για τα συνεζευγμένα οιστρογόνα. Επιπλέον, 22,3 εκατομμύρια συνταγές γράφηκαν για τα σκευάσματα συνεζευγμένων οιστρογόνων με οξική μεδροξυπρογεστερόνη.

Οι ενδείξεις της Θεραπείας Ορμονικής Υποκατάστασης σύμφωνα με τον Οργανισμό Τροφίμων και Φαρμάκων των ΗΠΑ (FDA) είναι: 1. αντιμετώπιση των μέτριων και των σοβαρών αγγειοκινητικών διαταραχών της εμμηνόπαυσης, 2. αντιμετώπιση της ατροφίας του αιδοίου και του κόλπου, και 3. πρόληψη της μετεμμηνοπαυσιακής οστεοπόρωσης. Κανένα σκεύασμα συνδυασμού οιστρογόνου/ προγεσταγόνου δεν έχει εγκριθεί από τον FDA για την πρόληψη της στεφανιαίας ή οποιασδήποτε άλλης νόσου της καρδιάς.

Τα τελευταία χρόνια, βάσει επιδημιολογικών δεδομένων, σκευάσματα οιστρογόνου ή οιστρογόνου/ προγεσταγόνου έχουν γραφεί για την πρόληψη της στεφανιαίας νόσου σε μετεμμηνοπαυσιακές γυναίκες. Οι τυχαιοποιημένες, μακροχρόνιες, μελέτες ΘΟΥ έναντι εικονικού φαρμάκου, για την επίπτωση της ΘΟΥ στην εμφάνιση καρκίνου ή καρδιαγγειακών νοσημάτων είναι: 1) Heart and Estrogen/progestin Replacement Study (HERS), 2) Estrogen in Venous Thromboembolism Trial (EVTET), 3) Women's Estrogen for Stroke Trial (WEST), 4) Women's Health Initiative (WHI), 5) Oestrogen in the Prevention of Re-Infraction Trial (ESPRIT-UK), και 6) Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM). Τα αποτελέσματα των τεσσάρων από αυτές τις μελέτες έχουν δημοσιευθεί (EVTET, WEST,

HERS, WHI), ενώ τα αποτελέσματα των δύο (ESPRIT-UK, WISDOM) αναμένονται.

Τα συγκεντρωτικά αποτελέσματα των τεσσάρων μελετών για τις επτά σημαντικότερες παθήσεις ύστερα από τη χορήγηση ΘΟΥ είναι: (1) ca μαστού (HERS, WEST, WHI) σχετικός κίνδυνος 1,27, (2) ca ενδομητρίου (HERS, WHI) 0,76, (3) ca παχέος εντέρου (HERS, WHI) 0,64, (4) στεφανιαία νόσος (HERS, WEST, WHI) 1,11, (5) εγκεφαλικό επεισόδιο (HERS, WEST, WHI) 1,27, (6) πνευμονική εμβολή (HERS, EVTET, WEST, WHI) 2,16, και (7) κάταγμα αυχένα μηριαίου (HERS, WEST, WHI) 0,72.

Τα μηνύματα που πρέπει να ληφθούν από αυτές τις μελέτες είναι: 1. Η απόφαση για την έναρξη ή τη συνέχιση της ΘΟΥ πρέπει να εξατομικεύεται, αφού ληφθούν υπόψη οι ωφέλειες και οι κίνδυνοι της θεραπείας, καθώς και οι εναλλακτικές θεραπείες. Όπως συμβαίνει με όλα τα φάρμακα, πρέπει να χορηγείται η χαμηλότερη δραστική δόση. 2. Εφόσον η γυναίκα αισθάνεται ότι ωφελείται από τη χρήση της ΘΟΥ, αλλά ανησυχεί για τα αποτελέσματα της WHI, δεν υπάρχει λόγος για άμεση διακοπή της θεραπείας. Εντούτοις, πρέπει να συζητήσει τις πληροφορίες αυτές και τις ανησυχίες της με το θεράποντα γιατρό της.

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