Million Women Study Collaborators. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet. 2007;369:1703–1710.

Narod SA. Ovarian cancer and HRT in the Million Women Study. Lancet. 2007;369:1667–1668.

Q. Does menopausal HRT increase the risk of ovarian cancer?

A. Maybe. Current users of hormone replacement therapy (HRT) were significantly more likely to develop ovarian cancer, and to die from it, than never users were. Specifically, 5 or more years of current HRT use resulted in 1 additional case of incident ovarian cancer for every 2,500 users and 1 additional death from ovarian cancer for every 3,300 users. Past HRT users had no elevation in risk.

EXPERT COMMENTARY

Andrew M. Kaunitz, MD, Professor and Assistant Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Jacksonville, Fla. Dr. Kaunitz is a member of the OBG MANAGEMENT Board of Editors.

***FAST** TRACK*

Five or more years of unopposed estrogen or combination HRT may increase the risk of ovarian cancer

Although rare, ovarian cancer usually is diagnosed late; for this reason, it is the most lethal gynecologic cancer in the US. In the Million Women Study, a massive cohort study carried out in the United Kingdom, roughly 950,000 postmenopausal women were surveyed between 1996 and 2001 and approximately 3 years later. Participants had no history of bilateral oophorectomy or ovarian cancer upon entry into the trial. Of these women, 50% had never used HRT, 30% were current users, and 20% had used it in the past. Over the course of the trial, 2,273 ovarian cancers were diagnosed, and 1,593 women died from the disease.

Elevated risk after 5 years of use

Compared with never users, women who had currently used HRT for longer than 5 years had a higher risk of 1) being given a diagnosis of (relative risk [RR], 1.20; 95% confidence interval [CI], 1.09–1.32) and 2) dying from (RR, 1.23; 95% CI, 1.09–1.38) ovarian cancer. However, current users with less than 5 years of use had no significantly elevated risk.

Other studies have suggested an association between HRT and ovarian cancer, but most have lacked power to determine the incidence of this rare malignancy. Although both estrogen-only and combination HRT were associated with ovarian cancer in current users in this trial, the findings are otherwise similar to those in regard to HRT and incident breast cancer.[1] In the WHI, there was no elevated risk of breast cancer when a woman used combination HRT for less than 5 years.[2]

Some will choose to counsel women about possible elevated risk

Because the Million Women Study is an observational study, with HRT exposure reported by participants, selection bias is possible (ie, respondents with ovarian cancer may be more likely to report HRT use). With this caveat, some clinicians may choose to counsel women that more than 5 years of unopposed estrogen or combination HRT may increase the risk of ovarian cancer, just as combination HRT raises the risk of breast cancer. A shorter duration of HRT does not appear to increase the risk of ovarian cancer and will probably serve the needs of many symptomatic, newly menopausal women.

References

1. Collins JA, Blake JM, Crosinani PG. Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update. 2005;11:545-560.
2. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas. 2006;55:103–115.

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Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465–1477.

Q. Does time since menopause determine how HRT affects cardiovascular health?

A. Maybe. In this secondary analysis of Women's Health Initiative (WHI) data, women who began HRT nearer to time of menopause had a lower risk of coronary heart disease (CHD) than did women who began HRT more distant from menopause, and whose risk was elevated. The trend was not statistically significant, however. On the other hand, the risk of stroke was significantly elevated for all women—regardless of when HRT was begun.

EXPERT COMMENTARY

Anthony A. Luciano, MD, Professor of Obstetrics and Gynecology, University of Connecticut School of Medicine, Center for Fertility and Women's Health, New Britain, Conn.

***FAST** TRACK*

Women who began menopausal HRT at a younger age and closer to menopause had a lower risk of heart disease

The putative protective effects of HRT on the risk of cardiovascular disease (CVD) suggested by observational studies for many years[1] were completely negated by prospective, randomized trials.[2,3] The WHI clinical trials reported no benefits with unopposed estrogen and a statistically significant greater risk of CVD events with combination HRT (odds ratio [OR], 1.24; 95% confidence interval [CI], 1.00–1.54).

The divergent results between observational studies and clinical trials have been attributed to several potential confounding factors, including methodologic differences such as healthy-use bias, compliance bias, and incomplete capture of early clinical events, or biological differences such as formulation and dose of the hormone regimen, time since menopause, and stage of atherosclerosis.[4]

Interestingly, observational studies of HRT in menopausal women have been remarkably consistent with randomized studies in predicting other risks, such as stroke, breast cancer, and thromboembolic events, as well as the benefits associated with HRT in regard to osteoporosis-related fractures and colon cancer. There is apparently something unique about CHD that accounts for divergent results between observational and controlled studies.

Earlier data suggested HRT is better suited to younger women

Rossouw and colleagues address 2 confounding factors—years since menopause and age of subjects when they started HRT—to explore the possibility that HRT may protect against CVD in younger, healthier women and be hazardous in older women who have preexisting cardiovascular disease. Support for this hypothesis comes from several sources, including animal studies and controlled and observational studies in postmenopausal women.

For example, in observational studies such as the Nurses Health Study, which consistently reported HRT-related protective effects on CVD, the postmenopausal women were younger (between 30 and 55 years old) and leaner (mean body mass index [BMI], 24.3) and had begun using hormones within 2 years after menopause.[5] They were, overall, quite different from the menopausal women in the WHI, who were older (mean age, 63 years) and heavier (mean BMI of 28.5) and who had been menopausal for about 10 years at the time of enrollment, when they started using HRT.[2]

Findings confirm greater hazard for women well past menopause

Rossouw and colleagues conducted secondary analyses of data from the 2 WHI randomized trials, looking at the effect of

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HRT on CHD and stroke across categories of age and years since menopause. They found that:

- Among younger women with less than 10 years since menopause, the hazard ratio (HR) for CHD was 0.76 (CI, 0.50–1.16), compared with 1.10 (CI, 0.84–1.45) and 1.28 (CI, 1.03–1.58) for the older groups with, respectively, 10 to 19 and more than 20 years after menopause
- The effects of HRT on total mortality tended to be more favorable in younger women than in older women (*P* for trend, .06)
- The presence of vasomotor symptoms at baseline had a significant impact on the increased risk of CHD with HRT in women age 70 to 79 years or in women with 20 or more years since menopause—but not in the younger group
- HRT increased the risk of stroke by 32%, regardless of age and years since menopause.

In younger women, hormones are a reasonable, short-term option

These secondary analyses of WHI data help us understand the divergent results between observational and controlled studies on the effects of HRT on CHD risk in postmenopausal women, and confirm the hypothesis that the health consequences of HRT may vary by distance from menopause, being absent in women close to menopause but significantly high in women distant from menopause, especially if they have vasomotor symptoms.

These data offer some reassurance that, in younger women, hormones remain a reasonable option for short-term treatment of menopausal symptoms but do not necessarily imply an absence of harm, especially over prolonged use.

Limitations of the trial

Although Rossouw and colleagues explore 2 important confounding variables, they did not address others, such as characteristics of study populations (such as estrogen levels) or different hormone regimens, which may be equally, if not more, important in determining the risk–benefit ratio of HRT in menopausal women. It is possible that women who have a lower BMI and who have a lower level of endogenous estrogen may constitute a group that benefits uniquely from hormone use, as a large cohort study of 290,827 postmenopausal women has suggested .[6]

It also may be that a different progestin may further reduce the CHD risk by inducing a better lipid profile, reducing plaque formation, and diminishing coronary artery reactivity and blood flow.

Clinical recommendation

These new data do not alter the current recommendation that HRT be used for the relief of disturbing vasomotor symptoms at the lowest effective dose and for the shortest tolerable time.[7]

However, we still have much to learn about the use of hormones in postmenopausal women, and need additional studies designed to allow us to develop the hormone regimen with the best safety and efficacy profile, which should be applied to the subgroups of postmenopausal women that will derive the most benefit. ■

References

1. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health. 1998;19:55–72.
2. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998;280:605–613.
3. Manson JE, Hsia J, Johnson KC, et al. Women's Health Initiative Investigators. Estrogen plus progestin and risk of coronary heart disease. N Engl J Med. 2003;349:523–534.
4. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on menopausal hormone therapy. N Engl J Med. 2003;349:645–650.
5. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med. 1996;335:453–461.
6. Rodriguez C, Calle EE, Patel AV, Tatham AM, et al. Effect of body mass on the association between estrogen replacement therapy and mortality among elderly US women. Am J Epidemiol. 2001;153:145–152.
7. ACOG Task Force on Hormone Therapy. Hormone Therapy. Obstet Gynecol. 2004;104(Suppl):1S–131S.

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Familiar refrain: Prescribe HRT at lowest dose and for shortest possible time