Decisions by the "Hormone Replacement Therapy" Consensus Group of the Turkish Society of Menopause and Osteoroposis & the Turkish Society of Gynecology

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In a meeting organized in Abant, Bolu, on 23 and 24 November, 2002, where Prof. Dr. Erdoğan Ertüngealp acted as the chairperson and 14 academicians from various Turkish universities participated in, the Turkish Society of Menopause and Osteoroposis asssessed the recent developments in the field of hormone replacement therapy (HRT) and made the following decisions with an unanimous vote.

1. Menopause: Background Information

The menopause is a state characterized by the permanent cessation of menstruation and the termination of the ovarian functions (those related to both reproduction and estrogen production) in a woman. The age of menopause is about 47 years in our country.

As a result of the increases occurred in the mean duration of life, the time period women live after the menopause has also increased.

Complaints presented by postmenopausal women may be classified as short- and long-term complaints. Hot flashes, sweat, insomnia, mood changes, concentration and memory problems, and difficulties related to sexual life which are experienced in most cases in the short term (especially in the first 5 years) have very unfavorable effects on the woman's life quality. Within the first few years after the menopause, vaginal and urinary atrophy associated with estrogen deficiency may also develop. In the long term, losses in bone mineral density (osteoporosis) may ensue and fractures may occur easily.

2. WHI Study

The results of the "Women's Health Initiative" (WHI) study conducted in the U.S. by the National Institute of Health (NIH) were published in the *JAMA* in July 2002. The results ot this study is briefly presented below:

Purpose of the study

- To investigate the significant benefits and risks associated with long-term HRT use.

Study design

- The mean age of the patients was 63 years (range, 50 to 79 years); 33% of the cases were between 50 and 59 years of age.
- It was conducted on a total of 16 608 women in 40 centers in the USA.
- It was conducted in a prospective, randomized, double-blind, placebo controlled design and it was planned for a period of 8.5 years, but terminated within 5.2 years.
- As the study drug, continuous combined conjugated estrogens 0.625 mg+medroxyprogesteron acetate 2.5 mg/day were used.

Unfavorable Results

- Breast cancer (In women who did not receive the active drug, 30 cases of cancer was observed per 10 000 women annually, while this figure increased to 38 cases in women taking the active drug; i.e., there were 8 more cancer cases per 10 000 women annually).
- Heart attacks (an increase from 30 cases to 37 cases per 10 000 women annually).
- Strokes (an increase from 21 cases to 29 cases per 10 000 women annually).
- Blood clots in deep veins (an increase from 16 cases to 34 cases per 10 000 women annually).

Favorable Results

- Colon cancer (a decrease from 16 cases to 10 cases per 10 000 women annually).
- Hip fractures (a decrease from 15 cases to 10 cases per 10 000 women annually).

No differences were found between the two groups in terms of all-causes deaths.

Evaluation of the Study

a) The mean age of of the women enrolled in the study was 63 years, 45.3% of the cases being over 59 years of age and 21%, over 70 years of age.
b) The mean body mass index (BMI) of the women enrolled in the study was 28.5 kg/m^2.
c) Approximately one-fourth of the cases had received hormone replacement therapy for varying durations before enrolling in the study.
d) Of the cases, 36% had hypertension, 13% had hyperlipidemia, 11% were smokers, 7% had a story of cardiovascular illness, and 4% had diabetes.
e) As compated with the control group, the frequency of breast cancer did not increase in the study group who had not received HRT previously, whereas there occurred an increase observed in the cases of breast cancer depending on the increased duration of HRT use.

f) In this study, the principal indications of hormone replacement therapy (hot flashes, urogenital atrophy, and life quality associated with them) have not been studied.

3. Recommendations for the current usage areas of HRT

A. What are the current usage areas for HRT?

a) Vasomotor symptoms (hot flashes, etc.)
b) Genito-urinary atrophy (vaginal dryness, lower urinary irritation, etc.)
c) Prevention of osteoporosis

Currently, there are no other choices as effective as hormone replacement therapy for hot flashes and genito-urinary atrophy.

B. Heart attack

a) According to the WHI study, HRT should not be used for merely cardioprotecion in those cases who do not have a history of heart disease.
b) In two other studies (HERS: Heart and Estrogen Replacement Study and HERS II), hormone replacement therapy failed to offer protection from heart disease in those cases who have a history of heart disease. In these two studies, neither an increase nor a decrease was reported in the risk for developing another heart disease in those cases who have a history of heart disease.
c) According to these three studies, whether the patients have heart disease at the baseline or not, some measures other than HRT use (diet, smoking cessation, exercise, use of statins, etc.) should be taken to prevent heart attacks and if necessary, a specialist in this field should be consulted.

C. What is the duration of safe HRT use with respect to breast cancer?

The period which is safe in terms of the development of breast cancer shows individual variations. Consistently with the previously-known data, an increase was reported in the risk of breast cancer in the HRT arm of the WHI study. The decision to continue HRT for a longer period should be made by the patient and the physician by weighing possible benefits with risks.

D. Should current HRT users discontinue therapy?

The adverse risks (absolute risks) observed in the WHI study are extremely low. Therefore, it is not necessary for the current HRT users to panic and stop their medication. In light of the above described data, however, the duration for continuing the therapy should be determined individually.

E. What should our approach be towards the prevention of osteoporosis?

HRT still maintains its importance for the prevention of osteoporosis. Biphosphonates and SERMs (selective estrogen receptor modulators) may also be used for the prevention of osteoporosis. However, when making an evaluation on the bone mineral loss, it should be noted that we do not have any data available related to the Turkish female population.

F. What should our approach be towards the hysterectomized cases receiving estrogen alone (ERT)?

Only the estrogen+progesteron therapy arm of the WHI study is terminated. Since the above-mentioned increase in risk is not observed in the study arm of the hysterectomized women on estrogen alone, this study arm is continuing.

G. Are the results of the WHI study also true for other types of hormone preparations and routes of administration?

In the WHI study, oral doses of conjugated estrogens 0.625 mg+medroxyprogesteron acetate 2.5 mg/day were used as the study drug. The results of the WHI study cannot be extrapolated on other types, dosages, and routes of administration of estrogens/progestins. Prospective, randomized, rigorous studies are needed for other types, dosages, and routes of administration of estrogens/progestins.

Recommendations

1. Currently, there are no other choices as effective as hormone replacement therapy for vasomotor disturbances and genito-urinary atrophy.
2. HRT should not be used solely for primary and secondary CV protection.
3. HRT still retains its importance for the prevention of osteoporosis. However, it should be ensured that exercise, calcium, and sunlight are utilized during the menopause.
4. According to the available data, there is no consensus on the duration of postmenopausal HRT use. However, with respect to breast cancer, patients should undergo an individual assessment for periods longer than 4 years.
5. At present, the lowest doses possible, which are effective in eliminating vasomotor complaints, should be preferred for HRT. Any preparation with a dose lower than the standard is not available yet.
6. The risk of breast cancer associated with HRT is not different from that associated with such factors as alcohol consumption, excessive body weight (BMI >30), first delivery being after the age of 30 years, and late menopause.
7. Increased risk of breast cancer associated with HRT disappears within 5 years following the discontinuation of the treatment.
8. The above-listed recommendations do not cover early menopause (that before 40 years of age), perimenopause, and surgical menopause.
9. In postmenopausal women, the balance of benefits and risks and cost of HRT should always be considered.
10. Whether they have any complaints or not, whether they are on HRT or not, women between 40 and 65 years of age should be under the supervision of the relevant specialist.