
**TURKISH SOCIETY OF
MENOPAUSE AND OSTEOPOROSIS**

“Hormone Therapy”

Consensus Results

4 -5 October 2003

ISTANBUL, TURKEY

Turkish Society of Menopause and Osteoporosis

“Hormone Therapy” Consensus Group Decisions

Turkish Society of Menopause and Osteoporosis has evaluated the latest developments on hormone therapy in a meeting attended by 23 scientists from various Turkish Universities and chaired by Prof. Dr. Erdoğan Ertüngealp on October 4-5, 2003 in Istanbul.

Turkish Society of Menopause and Osteoporosis issued a consensus report (November 2002) based on the data of “*Women’s Health Initiative (WHI)*” study supported by *NIH-USA* and published in July 2002 issue of *JAMA*. Due to recent developments on hormone therapy over the last year (multiple publications and re-analysis of *WHI* and “*Million Women Study*” published in *Lancet* 2003; 362:419-427), Turkish Society of Menopause and Osteoporosis provided following proposals derived from the consensus meeting on the present application of hormone therapy.

Terminology

ET	estrogen therapy
EPT	combined estrogen progesterone therapy
HT	hormone therapy (ET or EPT)
Systemic ET/EPT	ET/EPT preparations with predominantly systemic effects
Local ET/EPT	ET/EPT preparations with predominantly vaginal effects
Progestogen	progesterone (natural) and progestins (synthetic)

The Million Women Study

Aim of the study:

The study, designed to investigate the effects of various types of hormone therapies on breast cancer incidence on approximately one million post-menopausal women from UK, was published in the August 9, 2003 issue (*Lancet* 2003; 362:419-427) of the *Lancet* journal.

Study design:

- Large scale observational survey study
- The effect of various types of hormone therapies on the breast cancer incidence in approximately one million British women, aged between 50 and 64 years, living in UK, registered to the “National Breast Cancer

Screening Program”, and undergoing mammographic examination every three years, was investigated.

- Observation period: approximately 5 years (1996-2001)
- The study was conducted by evaluating the questionnaire forms comprised of different types of questions answered by the participants at their homes and brought in, with a computer program. The patient that completed the first questionnaire during inclusion to the study, brought a completed second questionnaire during her mammography visit on the third year.

Results of the study:

- According to the results of the *Million Women Study*, increase in the breast cancer risk is independent of HT route of administration (oral, transdermal, or implant), HT content (estrogen-progesterone types, tibolone), or therapy regimens (intermittent/continuous). The data derived from the *Million Women Study* have revealed that:
 - The relative breast cancer risk increases with HT.
 - This increase is observed to be higher with EPT (RR* =2.00) than with ET (R = 1.30).
 - The breast cancer risk also increases more with tibolone (RR= 1.45) than ET but not as much as EPT.

It has been suggested that increase in breast cancer incidence with HT occurs in the first 1 or 2 years.

Cumulative breast cancer incidence in 1.000 women aged 50 to 65

No HT use	5 year - HT use	10 year - HT use
32	ET (RR=1.30) 33.5 (+1.5 cases)	37 (+5 cases)
	EPT (RR=2.00) 38 (+6 cases)	51 (+19 cases)

The results of the Million Women Study. ET: Estrogen, EPT: Estrogen Progesterone. Compared to 32 breast cancer cases seen in women 50-65 years old with no HT use, there was an increase of 1.5 for a total of 33.5 cases in 1,000 women with a history of 5 year HT use, and an increase of 5 for a total of 37 cases in 1,000 women with a 10 year history of HT use. The relevant figures for EPT were 38 (+6) with 5 years of use and 51 (+19) with 10 years of use.

- The increase in the breast cancer risk due to HT use diminishes 5 years following the discontinuation of therapy.

*RR: Relative increased risk

Evaluation of the study:

- Even though the study is a large-scale prospective one, it is a non-randomized and observational survey study.
- There are major differences between the questions of the first and second questionnaires.
- The long 3-year-duration between mammographic examinations is questionable. Lack of yearly screening might cause some breast cancer cases to be undetected.
- The study has shown that breast cancer incidence tends to increase immediately in the first 1-2 years. This is in contradiction with the previously known data. The follow-up periods (average follow up for breast cancer incidents is 2.6 years and death from breast cancer is 4.1 years) for various end points are too short.
- In the study, a third of the women were administered different types of hormone therapies; however the last medication the patient took was recorded without mentioning the reason for switching. This kind of assessment raises serious doubts on the validity of data.

SUGGESTIONS:

- Currently, no other alternative therapy as effective as HT is available for the treatment of menopausal symptoms (vasomotor disorders and related sleep disturbances) and genitourinary atrophy.
- EPT should not be used solely for the primary and secondary cardiovascular protection. For ET, evidence still does not exist on this subject.
- No adequate data exist on the various patterns of progesterone use (long term progesterone [every 3-6 months for a 12-14 day period], intra-uterine devices including progesterone, or low dose estrogen without progesterone) of progesterone for the protection of endometrium.
- The increased breast cancer risk due to HT usage is not significantly different from other risk factors such as alcohol use, obesity (**BMI >30), first child-birth after the age of 30, and late menopause.
***BMI: Body Mass Index (weight[kg]/height²[m])*

- The efficacy of EPT in the prevention of osteoporosis and osteoporosis-related fractures is proven. Bisphosphonates, SERMs, and calcitonins can also be used in the treatment of osteoporosis. In addition, daily exercise, calcium intake and exposure to sunlight are very important during pre- and post menopausal period. However, it should be stressed that no adequate data on local population are available for the proper evaluation of bone mineral loss in Turkish women. Except for special cases, the analysis of bone mineral density every two years seems to suffice.
- No consensus appears for the duration of EPT use in the post-menopausal period. However, within the context of breast cancer risk, each case should be individually assessed for the continuation of EPT over 5 years. Based on current data, there seems to be no time limit for unopposed estrogen treatment (ET).
- No time limit is suggested by the current data on HT administration for premature ovarian failure (premature menopause) and early surgical menopausal cases.
- Lowest possible post-menopausal hormone therapy dosages (doses lower than 0.625mg for conjugated estrogens, lower than 1mg for micronized 17- β -estradiol, and lower than 0.05mg for transdermal 17- β -estradiol) should be preferred. Currently, lower-than-standard doses are not available in our country.
- Risk-benefit assessment and cost analysis should always be considered before administering hormone therapy to post-menopausal women.
- Given the data, hormone therapy to postmenopausal women should be prescribed on an “individual” basis.

Participants (in alphabetical order)

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Wishing you many
healthy and happy years



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