Proposal for deletion of ethinylestradiol as a therapy for menopausal symptoms and osteoporosis prophylaxis in women from WHO Model List of Essential Medicines

Submitted by the Department of Reproductive Health and Research
1 February 2011

Comments on evidence summary:

The introduction section clearly states the purpose of preparing the review and offers a comprehensive overview of the role and properties of the steroid hormone, estrogen, along with its pharmaceutical history and use for contraception and hormone therapy. Current clinical indications for using estrogens, along with contraindications and precautions, and commonly reported adverse events associated with estrogen therapy are included.

From a methodological perspective, the search strategy applied appears appropriate and thorough. Additional explanation on the criteria for considering clinical trials that were not randomized controlled trials (RCTs) as 'relevant' for inclusion in the review would have been helpful.

It would have been helpful to provide greater detail on the results observed among women who received either 10 or 50 mcg EE in the studies identified. Outcome information presented in the two tables was difficult to review; for example, results from the Speroff trial in Table 1 do not appear to offer any outcomes related to menopausal symptoms for women taking 10 mcg EE. However, this trial provides outcome information for osteoporosis prevention (for Table 2). In addition, it would be useful to know how long the women participating in this trial received treatment and were followed. In the instance of osteoporosis prevention, reporting how bone density was measured would have been informative.

While useful to search for systematic reviews on the topic, the exercise here illustrates that only three studies examined the dosages in question. The systematic review by Doren et al. does not present any new evidence. The table could more clearly highlight that this review only included one study - which has already been discussed - that examines one of the estrogen doses of interest.

The assessment of bias highlights the methodological limitations of the studies eligible for inclusion in the review, and underscore the limitations of the available evidence. Further, the review authors note that alternative therapies are currently available for osteoporosis treatment and the prevention of menopausal symptoms.

The conclusions drawn from the summary of published data on the topic are sound and appropriate.
Response to the proposal:

Ethinylestradiol is currently listed on the WHO Model List of Essential Medicines as a medicine used for contraception, hormone replacement therapy and osteoporosis treatment.

As part of the World Health Organization's effort to improve access to quality of care in family planning, two evidence-based guidelines - the Medical eligibility criteria for contraceptive use (MEC) and the Selected practice recommendations for contraceptive use (SPR) - were developed to provide guidance regarding 'who' can use contraceptive methods safely and 'how' to use contraceptive methods safely and effectively (WHO 2010, WHO 2005). Within these two guidelines, WHO publishes recommendations on the use of contraceptive methods containing ≤ 35µg ethinylestradiol (EE) combined with synthetic progestogens for healthy women, as well as women with selected medical conditions and personal characteristics.

WHO's Department of Reproductive Health and Research does not promulgate recommendations on the use of doses of 10 µg EE or 50 µg EE for the treatment of menopausal symptoms or for osteoporosis prophylaxis. In 1994, the Department convened an expert Working Group to advise WHO on areas for research on the menopause. The report from this meeting offers recommendations on areas for research related to menopausal symptoms, epidemiology and treatment. However, recommendations on specific therapies and/or formulations to treat menopausal symptoms were not determined at this meeting. The most extensive sections of the report attempt to resolve some of the controversy surrounding the use of hormone therapy to reduce the risks of osteoporotic fractures and cardiovascular diseases while also answering the question of whether hormone therapy increases the risk of breast cancer, endometrial cancer, and other gynaecological cancers. Information ranges from advice on calcium and vitamin D supplementation for the prevention of osteoporosis, to estimates of the increase in relative risk of breast cancer among women using estrogens alone for different lengths of time.

During 21-25 March 2011, the 18th Expert Committee on the Selection and Use of Essential Medicines, which will convene in Accra, Ghana to determine whether peroral doses of 10 µg and 50 µg ethinylestradiol should remain listed on the WHO Model List of Essential Medicines for the treatment of menopausal symptoms and osteoporosis therapy. A systematic review of the published literature was prepared to evaluate the efficacy of 10 µg and 50 µg ethinylestradiol for such uses.

Following a comprehensive search of multiple bibliographic databases, limited data from only three clinical trials and one systematic review provided evidence to evaluate the efficacy of 10 µg and 50 µg ethinylestradiol for treatment of menopausal symptoms or osteoporosis therapy (two studies for osteoporosis prophylaxis, three studies on menopausal symptoms). Moreover, all of these studies were all published prior to 1997, and only one was deemed to be of high methodological quality. Assessment of bias within these studies highlighted a variety
of methodological limitations, particularly regarding unclear allocation concealment of treatment groups and incomplete outcome assessment in two of the three trials.

Regarding the use of EE for menopausal symptoms, among women with an intact uterus, one trial reported an unacceptably high level of endometrial hyperplasia among women assigned to take 10 µg EE, resulting in the cessation of this arm of the study. The other trial, among women who had previously undergone hysterectomy and bilateral oopherectomy, 50 µg EE was found to alleviate menopausal symptoms.

With respect to osteoporosis prophylaxis, one trial found that after two years, women who received 10 µg EE experienced an increase in bone mineral density above baseline levels at the start of the trial. Another trial, investigating the use of 50 µg EE over a two year period, reported the 50 µg EE-treated group did not experience a loss in bone density compared with women in the control group.

Owing to the limited evidence identified, which was published at least 15 years ago or more, it can be recommended that ethinylestradiol alone for the prevention of osteoporosis or treatment of menopausal symptoms in doses of either 10 µg or 50 µg, be removed from the Essential Medicines List for the following reasons:

- Peroral doses of EE at 10 µg have been shown to increase the risk of endometrial hyperplasia among women with an intact uterus,
- Peroral doses of 50 µg EE were observed to alleviate selected menopausal symptoms, however, this dosage of EE is too high for contraceptive purposes,
- Ethinylestradiol in peroral dosages of 10 µg or 50 µg do not feature in any guidelines produced by the Department of Reproductive Health and Research,
- Other more effective therapies are currently available for osteoporosis treatment, such as Conjugated Equine Estrogen, Bisphosphonates, and SERMs.

References

