The Million Women Study: what is missing?

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The main problem with an epic study like HERS, WHI and the Million Women [1] is the time-gap between the inception of the protocol until the release of its results. Long-term trials answer clinical questions that seemed relevant and important at baseline, reflecting the state-of-the-art knowledge pertinent to that period. In retrospect, the biggest flaw in planning WHI was to pick up the wrong population, and use the wrong drug. How often do we initiate nowadays hormone treatment to a 65- or 70-year-old lady? And if we do so, how often do we recommend a standard dose in such cases?

The lesson to be learnt is that we must look also beyond the published data, and ask ourselves what is missing in the results of any large-scale study that might have been as important. What sort of clinical queries should have been asked and resolved if the protocol would have been contemporay.

Indeed, the size of the Million Women Study is colossal. But its main finding that the combination of estrogen and progestin carries a higher risk for breast cancer than estrogen only—has already been reported in several previous studies. Also, the authors concluded that results varied little between specific estrogens and progestagens or their doses; or between continuous or sequential regimens, or different routes of administration. Fortunately, the investigators understood that we can no longer refer to the consequences of “hormone” therapy as one entity, nor should we talk of a “class effect”, but rather look for data of particular regimens. The article contains the results of several formulations (oral, transdermal and implanted), several constituents (all equine estrogens, all ethinylestradiols, medroxyprogesterone acetate, norethisterone, norgestrel, and tibolone), several dosages (above 0.625 mg equine estrogen, 0.625 mg or below; above 1 mg ethinylestradiol, 1.0 mg or below), type of regimen (sequential and continuous). However, in 2003 we would like to have even more detailed data, such as the specific risks of low-dose estrogen (25TTS, or 0.5 mg oral estradiol), and the specific risks for low dose progestins, either per a single dose or the accumulative dose per a “long cycle” (progestin given once in 2–3 months). Ideally, we should have safety data on each and every hormone preparation that we use. Such detailed data could help clinicians to individualize treatment and optimize it, considering both benefits and potential adverse events of therapy.

Another aspect, which was not covered sufficiently by the Million Women Study, relates to the histology and size of the tumors. In another recent publication of the WHI data, the authors claimed that breast cancers diagnosed in the estrogen plus progestin group were larger and at a more advanced stage compared with those diagnosed in the placebo group [2]. Such information is intriguing since previous studies usually showed that cancers in hormone users were less aggressive and having a better prognosis than those in never
users. Since the WHI population involved women around the age of 65–70, whereas the upper age at entry to the Million Women Study was 64, there might be a substantial difference in the development and the biology of estrogen-related breast cancers at different age groups. If these morphological and histological data are available to the Million Women Study investigators, it will be extremely important to publish it.

References