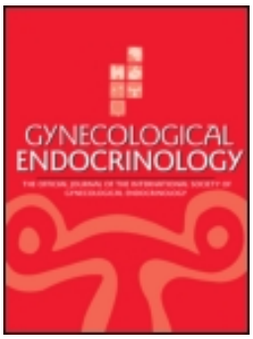

Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: informahealthcare.com/journals/igye20

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To cite this article: Frederick Naftolin, Jennifer King & John H. Morrison (2010) *Post hoc* magnetic resonance imaging cannot justify the conclusions of WHIMS, Gynecological Endocrinology, 26:6, 391-392, DOI: 10.3109/09513591003630229

To link to this article: https://doi.org/10.3109/09513591003630229

Published online: 23 Feb 2010.

Gynecological Endocrinology, June 2010; 26(6): 391–392

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EDITORIAL

Post hoc magnetic resonance imaging cannot justify the conclusions of WHIMS

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The Women's Health Initiative Memory Study (WHIMS) and WHIMS-MRI trials address the clinical effects of treatment with conjugated equine estrogen and medroxyprogesterone acetate (CEE and MPA, respectively; HT) begun in largely asymptomatic postmenopausal women at ages 65 and older [1–3]. Contrary to the meta-analysis of observational studies on peri-menopausal women who were given HT [4], both WHIMS reports indicate that estrogen and progestin have no preventive role in mild cognitive impairment and may in fact increase the risk for dementia [1–3]. It is not stressed that the WHIMS population was older and had many characteristics that would discourage HT.

In fact, the use of CEE and MPA in these trials does not reflect their use in current clinical practice and the outcomes in the WHI are not sufficiently well designed or documented to justify WHIMS' conclusions that may be drawn from remote post-treatment clinical or Magnetic Resonance Imaging (MRI) studies [5]. The WHIMS examined whether postmenopausal CEE with and without MPA would reduce the risk of mild cognitive impairment or dementia. The original trialists had been randomised to treatment, but only after the Women's Health Iniative (WHI) exclusion criteria had ensured that there was no representative initial subject population [5]. Nonetheless, based on their findings, WHIMS reported that estrogen alone or combined therapy did not prevent mild cognitive impairment and stated there was an increased risk for probable dementia in postmenopausal women aged 65 years or older receiving hormone therapy [1,2]. This work was followed by the WHIMS-MRI study, in which a subset of women aged 71–89 years who had participated in WHIMS trials received a post-study brain MRI. Scans demonstrated decreased frontal lobe and hippocampal volume in those women receiving hormone therapy when compared to placebo [3]. Both brain areas are involved in cognitive function and memory, with decreased hippocampal volume as a potential risk factor for dementia. However, before any conclusion can be drawn about whether the risks of estrogen plus progestin therapy outweigh the benefits, some issues needed to be addressed that in light of the exclusion criteria of the WHI could not be addressed. First, the randomisation process had no neurological exam, no brain imaging, no apolipoprotein E4 levels, and no assessment of family history of dementia. The only distinguishing factor between subjects was age. Second, as they were taken from the main WHI study, the WHIMS study participants were not reflective of the usual women in which hormone therapy is initiated [5]. Finally, whether or not the results of the MRI study are interpretable may be contested but their clinical inapplicability is not in question; asymptomatic women who are aged 65 or older should never be given HT at the usual clinical doses reserved for symptomatic women who are still in the first years of the menopause. Extension of conclusions from the WHIMS or the WHIMS-MRI study to clinical decisions regarding the use of HT in the treatment of symptomatic menopausal women is even further afield. The interpretation of this series of studies is further complicated by the agents and regimens utilised: the hormones administered were CEE plus MPA in constant doses [1–3]. While CEE has not been shown to be responsible for neuronal

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ISSN 0951-3590 print/ISSN 1473-0766 online
DOI: 10.3109/09513591003630229

damage in *in vitro* experiments, the type of progestin used may play an important role in risk [6–8]. This seems especially important in the case of MPA since it is known to have potent androgenic effects, including effects on lipoprotein and carbohydrate metabolism, which may play a role in vascular disease [7,8]. Finally, MRI was used to assess the total volume of the hippocampus and the frontal lobe and decreased volume was indicated to represent neurodegeneration [3]. However, because no pretreatment MRI scans were obtained, there is no possibility of a comparison to baseline brain volumes; at age 65 or older, there may have already been significant brain destruction present. Moreover, for interpretation, further studies should be done using functional MRI to rule out the possibility that the decreased volume is not secondary to pruning of non-eloquent brain. While hormone treatment may have adverse effects on an already diseased brain when it is administered long after menopause, further investigation is warranted before an opinion can be made regarding the neurotoxicity of estrogen and progestin in the WHI or WHIMS.

Acknowledgement

To Emma Steinberg for her assistance and helpful discussions.

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