

Hormone Replacement Therapy and Cardio- and Cerebrovascular Disease. The influence of risk factors.

Ph.D. thesis by Ellen Løkkegaard, MD

Department of Obstetrics and Gynaecology, H:S Hvidovre Hospital

Faculty of Health Sciences, University of Copenhagen

Based on the following three publications :

Increased risk of Ischaemic Heart Disease among Diabetic women using Hormone Replacement Therapy. Analyses based on the Danish Nurse Cohort Study.

Løkkegaard E, Pedersen AT, Heitmann BL, Jovanovic Z, Keiding N, Hundrup YA, Obel EB, Ottesen B. (BMJ, 22. February, 2003)

Increased risk of stroke in hypertensive women using Hormone Therapy. Analyses based on the Danish Nurse Study.

Løkkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Hundrup YA, Obel EB, Pedersen AT. (Archives of Neurology, October, 2003)

The validity of self-reported use of Hormone Replacement Therapy among Danish Nurses.

Løkkegaard E, Johnsen SP, Heitmann BL, Stahlberg C, Pedersen AT, Obel EB, Hundrup YA, Hallas J, Sørensen HT.

(In press Acta Obstetricia et Gynecologica Scandinavica)

A favourable influence of female sex hormones on cardiovascular disease is indicated by the lower incidence of cardiovascular diseases among women compared to men at the same age. At menopause the ovaries gradually stop the production of endogenous female steroid sex hormones. To alleviate menopausal symptoms, protect against osteoporosis, and potentially decrease risk of cardiovascular disease, hormone replacement therapy (HRT) has been widely used since the 1950s. When the present study was initiated, results from the observational literature on the associations between HRT and cardio- and cerebrovascular diseases suggested a considerable risk reduction of cardiovascular diseases, no effect on cerebrovascular diseases, and an increased risk of venous thrombo-embolic disease with HRT. However, the results from randomised clinical trials (RCT) appearing the last five years demonstrated no preventive effect of HRT on cardio- or cerebrovascular disease.

The aim of the present study was to investigate the risk of cardio- and cerebrovascular diseases among women using HRT, especially the potential modifying effect of presence of cardiovascular risk factor, and to determine whether there is a favourable effect of use of HRT immediately after menopause. An additional aim was to validate self-reported information on use of HRT against prescription based pharmaco-epidemiological registers.

The present study is a prospective cohort study based on Danish nurses: the Danish Nurse Cohort Study. In 1993 all female members of the Danish Nurse Association above 44 years of age were investigated with postal questionnaires and followed through individual linkage in National Registers of Hospital Discharges and Deaths (NPR) until the end of 1998. Using multivariate Cox-proportional-hazards analyses, we found no protective effect of HRT on total mortality, on the incidence of ischaemic heart disease, or on myocardial infarction. Rather, a consistent modification of the effect of HRT by the presence of diabetes was observed, implying a specifically increased risk of total death, ischaemic heart disease, and myocardial infarction among diabetic women, but not among non-diabetic women, taking HRT. We found no association between HRT and risk of total stroke. However, HRT (in particular the combined oestrogen/progestin therapy) was associated with an increased risk of subtypes of stroke including the non-fatal stroke, the ischaemic strokes, and especially the non-fatal ischaemic strokes. We found this increased risk to be based on a consistent increased risk of total stroke as well as on all the various subtypes of stroke among hypertensive female nurses using HRT. This risk was most pronounced among nurses using combined oestrogen/progestin therapy. Normotensive nurses using HRT showed no increased risk of stroke in this study.

Early menopause was found to be a risk factor for ischaemic heart disease, which is not reduced by use of HRT. When the early menopausal women were divided into two groups based on whether menopause was surgically induced or naturally occurring, however, HRT was associated with a significant reduction of the increased risk among the surgically menopausal women. We considered the quality of the exposure measure by comparing self-reported information on use of HRT to prescription based pharmaco-epidemiological registers for nurses living in two Danish counties and found acceptable validity of self-reported use of HRT. Our data potentially suggest explanations for the diverging results from the observational literature and RCT. The observational literature is affected by severe healthy user bias among users of HRT in countries with no free access to medical care, a bias not present among Danish nurses using HRT. In the RCT, however, bias may occur due to people willing to accept randomisation and continue treatment over time and thus not be representatives of the general population. Also the randomised studies may be influenced by the presence of diabetes and hypertension. Our findings need to be confirmed in other studies

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