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Blood pressure in middle-aged women. Influence by hormonal situation. Results from the Women's Health in Lund Area (WHILA) Project

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## **BLOOD PRESSURE IN MIDDLE-AGED WOMEN.** INFLUENCE BY HORMONAL SITUATION. RESULTS FROM THE WOMEN'S HEALTH IN LUND AREA (WHILA) PROJECT

#### SESSION 1: POSTMENO-PAUSAL LIFE: RISK AND CHANCES

## INTRODUCTION

Cardiovascular disease in women increases after the menopause and approaches the risk of men. This observation suggests that loss of ovarian function contributes to the overall increase in risk. The risk of cardiovascular disease is multifactorial and estrogens have been shown to have beneficial effects on several intermediate risk markers for cardiovascular disease and hormone replacement therapy has been shown to prevent myocardial infarction in women in several cohort and case control studies. In secondary prevention, observational data showing a benefit and a randomised clinical trial showing no difference suggest that additional information on the relative importance of female gonadal hormones in cardiovascular disease must be further investigated.

High blood pressure is associated with an increased risk of cardiovascular disease and is closer linked to the risk of stroke than to myocardial infarction. Observational studies on stroke and HRT are conflicting [1]. Some show a benefit, others show no difference, but none indicate an increased risk by HRT. Results on blood pressure are also to some extent conflicting, but agree on the point that changes in blood pressure by female gonadal hormones are generally small. To further outline the impact on gonadal hormones on cardiovascular risk factors, including blood pressure, large studies are needed, which could be stratified for potential

confounders, such as body weight, smoking etc. Ideally different HRT regimens should be dealt with separately as type, dose and mode of administration of both the estrogen and progestogen components of HRT regimens are of importance for the metabolic effects and conceivably also on blood pressure.

However, there are a number of experimental data both in animals [2, 3] and in man [4] which render estrogen interesting especially for certain subgroups of women at risk for hypertension or as adjunct therapy when treating hypertension in women. But oral estrogens have also been demonstrated to increase serum levels of angiotensinogen which in turn may aggravate blood pressure elevation. In order to further delineate these issues it is of importance to recognise the determinants of high blood pressure in middle aged women.

### MATERIAL AND METHODS

The Women's Health in Lund Area Study is a population-based observational study on women's health.

All women born between 1935 and 1945 (n = 10,870) who resided in the area of Lund on December 1, 1995 received a mailed questionnaire to participate in a health screening programme consisting of questionnaire based data on several issues of health and quality of life, use of various medications, diet, physical activity etc. All participants were asked to bring their questionnaire to the screening centre where a personal interview took place with each participant performed by a specially trained nurse midwife. Misunderstandings pertaining to the questionnaire and additional information on the participant's health could be added. Participants were also asked to join the routine mammography-screening programme.

Height, body weight and waist/ hip ratio were measured. A bone densitometry was carried out using DEXA-technique (Osteometer-200). Blood pressure was recorded twice in the right arm after 15 and 30 minutes rest in the seated position with a Mercury Sphygmomanometer with cuff size adjusted to the arm width. Korotkoff phase V was taken as a diastolic blood pressure. The average of the recordings measured to the nearest 2 mmHg was the blood pressure variable used. Venous blood samples were drawn for the analysis of serum lipids and lipoproteins, blood glucose. In addition, serum aliquots as well as whole blood were retained in -70 °C freezers for future analysis.

### STATISTICAL ANALYSIS

The Wilcoxon's rank sum test was used for the comparison of continuous variables and a chisquare test for testing the number of subjects in different groups. The statistical programme SPSS (statistical packages for the social sciences) and SAS (statistical analysis system) were used. A p-value of less than 0.05 was considered statistically significant.



### RESULTS

Results given below are based on the 5,000 first examined. At this time data are cross sectional. Mean systolic blood pressure was  $131 \pm 7$  mmHg. Diastolic blood pressure was  $85 \pm 9$  mmHg. 17 %had blood pressure above 160 mmHg systolic and/or 95 mmHg diastolic, in which figure the diastolic elevation was the most abundant one. We found a positive correlation between systolic as well as diastolic blood pressure and the 2 hours glucose value at the oral glucose tolerance test, which was also performed as a secondary screening measure. In this age group of 50 to 60 year old women some were still premenopausal (11 %), some were postmenopausal without hormone replacement therapy (54 %)and some postmenopausal women were using hormone replacement therapy (34 %). Endogenous as well as exogenous hormones seem to influence blood pressure so that women under hormonal influence had slightly lower blood pressure, especially of the diastolic compound. Although statistically significant these differences were small. In a sub-study carried out among the thousand first screened women, 32 postmenopausal women without HRT and 32 postmenopausal women with HRT were randomly selected to a 24-hour blood pressure measurement. The sub-study was designed to detect difference in diastolic blood pressure of 5 mmHg between the two groups with a power of 80 % and 5 % level of significance (two-tailed test). However, no difference could be detected, which further

underlines that the effect by female gonadal steroids on blood pressure is small.

### DISCUSSION

Blood pressure rises in both men and women with age and about 80 % of women above 75 years of age are hypertensive. In the study by Staessen et al. [5] women who were premenopausal had lower both diastolic and systolic blood pressure as compared to postmenopausal of corresponding age. The difference being about 2–5 mmHg in diastolic and 5-7 mmHg in systolic blood pressure. Our results are in accordance with the study by Staessen [5]. HRT given to women have yielded inconclusive result and HRT have either generated no change or a small decrease [6, 7] There is no evidence that HRT increases blood pressure, which is in contrast to the findings with oral contraceptives. Blood pressure lowering has been more consistent with transdermal than with oral administration of estradiol [8], which may imply that the inevitable increase in angiotensinogen by oral estrogens plays a role. This finding could be of clinical significance as in hypertensive women it would seem theoretically advantageous to combine a blood pressure lowering agent, which impacts on the angiotensinogenrenin system with estrogen therapy. Using this combination Weber et al. [9] were able to demonstrate that the ACE inhibitor, moexipril, had a more pronounced blood pressure lowering effect in women given HRT in comparison to those given placebo. However, the blood pressuring lowering effect by oestrogens is generally small, which may be part of the reason as to why it is difficult to demonstrate any beneficial effects by HRT on stroke, although some studies have demonstrated a reduction in women using HRT compared to non-users. It is an intriguing challenge to attempt to identify a subgroup of hypertensive women, who may benefit specifically from HRT alone or HRT in combination with antihypertensive medication.

Using the 24-hour measurements we were not able to detect any difference between HRT users and non-users. However, in a clinical trial Akkad et al. [10] demonstrated a lowering of blood pressure by both oral and transdermal oestradiol, which was particularly pronounced by the transdermal preparations and during the night.

In a recent prospective study by Szekacs et al. [11] a cyclic oral combination oestradiol and norgestrel given for 19 weeks reduced blood pressure in 34 women with treated hypertension as evidenced by ambulatory 24 h blood pressure measurements. This study also indicated that women treated with calcium channel blockers had only half the reduction compared with other blood pressure lowering regimens indicating a completion.

Experimental data would also imply that estrogens by themselves have a calcium channel blocking effect as well as some ACE inhibitory effect.

Our results are in agreement with a recent cross sectional multi cen-



tre study from Italy [12] in which 10,814 patients had elevated blood pressure. Having considered confounders such as age postmenopausal women not using HRT were at greater risk for hypertension than women on HRT. The Italian study further underlined the importance of overweight, family history, diabetes and hypertriglyceridaemia for the development of high blood pressure.

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#### Professor Göran Samsioe

Göran Samsioe obtained his bachelor of medicine in 1966 and qualified as a medical doctor at Göteborg University Medical School, Sweden in 1971. Shortly after this in 1974, he was awarded his PhD from the same university. After a few years of training, Professor Samsioe be-

came a specialist in obstetrics and gynecology and took the post of Assistant Professor in Obstetrics and Gynecology at Göteborg University in 1976. He was then later promoted to Associate Professor in the same department. He is very involved with the World Health Organization (WHO) and has set up a reference laboratory for them. He has also been responsible for internal and external quality control schedules for the WHO, and supervised multicenter clinical trials within the field of family planning. Presently, Professor Samsioe holds the position of Professor of Gynecological Endocrinology, at the University Hospital in Lund, Sweden.

Professor Samsioe is a member of numerous committees and is the founding member of several editorial boards including Osteoporosis International, Journal of the North American Menopause Society and The Journal of Menopause. He is also the author of over 400 papers on menopause, cardiovascular disease and lipid metabolism.

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