

## ABSTRACT

### **Polycystic ovary syndrome Ovarian pathophysiology and consequences after the menopause**

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The Polycystic Ovary Syndrome (PCOS) is an endocrine disorder affecting ~10% of women. It is characterized by oligo/anovulation, hyperandrogenism, and polycystic ovaries. PCOS is associated with acne, hirsutism, infertility, abdominal obesity, type 2 diabetes, hypertension and dyslipidemia, with the latter four being cardiovascular disease (CVD) risk factors.

The aims of the thesis were to study PCOS regarding ovarian pathophysiology and postmenopausal development concerning anthropometry, reproductive hormones, bone mineral density (BMD), fractures, CVD risk factors and events and mortality.

Ovarian (stroma and granulosa cells) expression in selected genes of PCOS/controls was analyzed by quantitative PCR, with special emphasis on inflammation. In the central stroma of PCOS ovaries, genes of five inflammation-related factors, one inflammation-related transcription factor and one growth factor were under-expressed. One growth factor and one coagulation factor were over-expressed. In the granulosa cells of the PCOS women, all of the differentially expressed genes were over-expressed (five inflammation-related, two coagulation-related, two growth factors, one permeability-related and one growth-arrest-related).

Thirty-five PCOS women (diagnosed 1956-65) and their 120 randomly allocated age-matched controls (from the WHO MONICA study, Gothenburg), were examined in 1987 regarding anthropometry, reproductive hormones, CVD risk factors, lifestyle factors, medication and medical history (via questionnaire) and for the present thesis re-examined in 2008 (mean age 70.3 years) with the same variables. BMD was assessed by single photon absorptiometry in 1992 and by dual energy x-ray absorptiometry at follow-up in 2008. The National Board of Health and Welfare Registry and the Hospital Registry provided information on morbidity and mortality.

The PCOS women still had higher free androgen index (FAI), but lower FSH than controls. Hirsutism, hypertension and hypertriglyceridemia were more common, but climacteric symptoms and hypothyroidism were less prevalent among the PCOS women. The higher waist/hip ratio among the PCOS women in 1987 could not be detected at follow-up, possibly due to an increase in hip circumference in the PCOS women and to an increase in weight among the controls. BMD, fractures, diabetes, CVD events, total mortality and cancer incidence were similar in the PCOS women and controls at follow-up.

In conclusion, the ovaries of the PCOS women showed differences in the expression of key proteins, with implications for PCOS-specific arrested folliculogenesis and OHSS risk. Late postmenopausal PCOS women were still hyperandrogenic and hirsute with persistent hypertension and hypertriglyceridemia. However, the incidence of fractures, diabetes, cancer, CVD morbidity and total mortality was similar to that of the general population. Differences in body composition had disappeared in the PCOS women compared with the controls during 21 years of follow-up.

*Key words: body composition, bone mineral density, cardiovascular disease, fracture, gene-expression, menopause, mortality, ovary, polycystic ovary syndrome, reproductive hormones*  
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## This thesis is based on the following papers:

- I. Differential expression of inflammation-related genes in the ovarian stroma and granulosa cells of PCOS women.  
Schmidt J, Weijdegård B, Mikkelsen AL, Lindenberg S, Nilsson L, Brännström M  
*Submitted.*
- II. Reproductive hormone levels and anthropometry in postmenopausal women with polycystic ovary syndrome (PCOS): A 21-Year follow-up study of women diagnosed with PCOS around 50 years ago and their age-matched controls.  
Schmidt J, Brännström M, Landin-Wilhelmsen K, Dahlgren E  
*J Clin Endocrinol Metab. 2011;96:2178-85.*
- III. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: A 21-year controlled follow-up study  
Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E.  
*J Clin Endocrinol Metab. 2011. Epub ahead of print Sept 28.*
- IV. Body composition, bone mineral density and fractures in late postmenopausal PCOS women – A long-term follow-up study  
Schmidt J, Dahlgren E, Brännström M, Landin-Wilhelmsen K  
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