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**Institutionen för Molekylär Medicin och Kirurgi, Karolinska  
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# Patients with hyperprolactinemia clinical and epidemiological perspectives

**AKADEMISK AVHANDLING**

som för avläggande av medicine doktorsexamen vid Karolinska  
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av

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## ABSTRACT

Hyperprolactinemia (HPL) is the most common endocrine disorder of the hypothalamic-pituitary axis and prolactinomas the most frequent pituitary tumour. A majority of the patients are women in reproductive age seeking health care for menstrual disorders or infertility. Because a majority of the patients are relatively young at diagnosis and the medical treatment often life-long, it is essential to study the efficacy of treatment and long-term results in these patients. Data are lacking in women with HPL concerning parity and there is still a void of studies evaluating cancer risk and whether the metabolic state is altered in patients with elevated prolactin (PRL) levels. This thesis, which contains four studies addressing these issues, is aimed to improve our knowledge and the quality of clinical management in patients with HPL.

*Long-term outcome of treatment:* A total of 271 women with HPL were retrospectively evaluated. At diagnosis, 87% of the women presented with menstrual disturbances and 47% had galactorrhea. The outcome after up to 29 years of clinical follow-up (median 9.3 years) showed a good treatment result with restoration of menses and galactorrhea in 94% of the women. Medical therapy with dopamine (DA) agonists normalised PRL levels in 71% of the patients and 80% had a total or partial degree of tumour reduction. Fifty-three per cent (9 of 17) of the surgically treated patients and one third (three of nine) of the patients treated with radiotherapy exhibited long-term normalisation of PRL levels without medical treatment.

*Parity and pregnancy outcome:* In this matched cohort study (271 women with HPL and 1084 comparison subjects) a reduced parity was found in HPL patients, mainly because there were more nulliparous women and fewer women with more than two children. Parity was inversely associated with HPL status ( $P$  for trend = 0.0009). No increased risk of pregnancy or delivery complications was found. In addition, outcomes of the newborns did not differ between patients and controls.

*Cancer risk:* A small, though significant, increased risk of overall cancer was found in 969 patients with HPL (668 women and 301 men) as compared with matched comparison subjects (hazard ratio [HR] 1.31; 95% CI 1.02-1.68) which was mainly due to increased risk of upper gastrointestinal cancer in all patients and hematopoietic cancer in females. Risk of breast cancer did not differ between patients and controls. Furthermore, a reduced risk of prostate cancer by 60% was found in HPL men (HR 0.40; 95% CI 0.16-0.99).

*Metabolic assessment:* Evaluation of 14 consecutive patients with prolactinomas (eight women and six men) before and after normalisation of PRL levels by DA agonist therapy revealed that HPL men had an unfavourable metabolic profile at diagnosis. After therapy, a significant decrease of body weight, waist circumference and body fat% was found in the men. A positive correlation between PRL levels and low-density lipoprotein (LDL) cholesterol at diagnosis was seen and LDL cholesterol decreased after 2 months of DA agonist treatment. Furthermore, peripheral insulin sensitivity evaluated with a euglycemic hyperinsulinemic clamp tended to improve after therapy. This improvement was associated with a reduction in PRL levels.

In conclusion, the results of this thesis show that HPL patients can be effectively treated with DA agonists in the long-term perspective and emphasise its role as first-line therapy. Women treated for HPL have a reduced parity, but there are no increased risks during pregnancy or for their offspring. The small increased risk of cancer that was found in HPL patients and the possible negative effect of elevated PRL levels on metabolic state need to be further evaluated; however, it implies the need for an active treatment approach and close follow-up of patients with HPL.

*Key words:* prolactin, hyperprolactinemia, dopamine agonist treatment, parity, pregnancy outcome, cancer risk, lipids, insulin sensitivity