The Effect of Residual Beta Cell Activity on Menstruation and the Reproductive Hormone Profile of Insulin-dependent Diabetics

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Summary. To investigate the cause of secondary amenorrhoea in insulin-dependent diabetes gonadotrophins, sex steroid hormone levels and residual beta cell activity (C-peptide index) were estimated in a group of 43 women with IDDM. Among 26 women with residual insulin secretion, the C-peptide positive (CpP) group, 5 had secondary amenorrhoea (CpP-Am); among 17 women without endogenous beta cell activity, the C-peptide negative (CpN) group 6 had secondary amenorrhoea (CpN-Am). In this study two different types of secondary amenorrhoea in insulin-dependent diabetics were observed. All CpP-Am women have the classical hormone profile of the polycystic ovary syndrome (increased (LH/FSH ratio, increased serum testosterone, decreased SHBG) together with a history of oligomenorrhoea and excess weight before the onset of diabetes. On the other hand, all CpN-Am women had decreased LH levels as well as low LH/FSH ratio and testosterone levels. These results strongly suggest that a lack of residual pancreatic beta cell activity influences hypothalamus-pituitary function in insulin-dependent diabetes. It might be concluded that PCOS is independent of diabetes while low LH amenorrhoea seems to be the consequence of diabetes and is strongly associated with a lack of residual insulin secretion.

Key words: Secondary amenorrhoea – Insulin-dependent diabetes mellitus (IDDM) – Residual beta cell activity – C-peptide – Gonadotrophins

Introduction

Reproductive failure occurs in laboratory animals with experimentally induced diabetes (Lawrence and Coutopulos 1960; Hunt and Bailey 1961; Liu et al. 1972). Menstrual disturbances in insulin-dependent diabetes have also been reported (Djursing et al. 1982, 1983) although no systematic study of this
disorder has been done. Mechanisms responsible for menstrual cycle disturbances in insulin-dependent diabetes have not been clarified. The present study examined the prevalence and type of secondary amenorrhoea according to gonadotrophin and sex hormone levels and residual beta cell activity in women with insulin-dependent diabetes.

**Material and Methods**

We studied 43 insulin-dependent diabetics. All fulfilled the following criteria:

- insulin-dependent diabetes mellitus of at least 3 years duration,
- no evidence of diabetic complications (except "background" retinopathy),
- no other illness or medications.

Each patient gave her informed consent for participation in the study. None of the patients had ketonuria. All were normotensive and had a normal serum creatinine.

At the time of testing the majority of the patients were in good or moderate diabetic control as judged by serum fructosamine concentrations and a 24 h blood glucose profile on the day of or day before study. Samples for blood glucose determinations were taken every hour.

Residual pancreatic cell activity was judged by the value of the C-peptide index (mean value of 4 samples taken every 6 h during a 24 h blood glucose profile) (Faber and Binder 1985).

According to their peripheral C-peptide level patients were subdivided into the following subgroups:

- C-peptide negative (CpN) – 17 patients with undetectable C-peptide (<0.09 nmol/L),
- C-peptide positive (CpP) – 26 patients with residual beta cell secretion.

Blood samples for hormone measurements were taken in the early follicular phase of the cycle or at any time in amenorrhoic women. Each value given in results represents the mean of at least two or three measurements. Blood glucose was measured by a glucose oxidase method.

All amenorrhoic patients had pelvic ultrasonography. Ovarian volume was calculated using the formula proposed by Sample et al. 1977. Body mass index (BMI) represents the ratio of body weight (kg) to height (m)².

Blood samples for hormone measurements were centrifuged and serum stored at −20°C. Serum hormone concentrations were determined by double antibody radioimmunoassay using Byck Mallinckrodt (C-peptide, prolactin), Serono-Biodata (LH, FSH, estradiol, testosterone) commercial kits. Serum SHBG was determined by using the Biodata commercial kit which is based on the method for indirect determination of SHBG through the evaluation of dihydrotestosterone binding capacity.

Statistical analysis of differences between the group were performed using Mann Whitney Wilcoxon Rank Sum test and by unpaired t-tests. Fuller analyses which simultaneously assessed the effects of C-peptide status and menstrual status on a series of hormone measurements involved nested analysis of variance (Armitage 1971) using the statistical package GLIM (Generalised Linear Interactive Modelling) (Baker and Nelder 1978).

**Results**

Of 43 of our insulin-dependent women eleven had secondary amenorrhoea of between 9 months and 4 years duration and the remaining 32 women had regular menstrual cycles (21 were C-peptide positive or CpP-Nc and eleven were C-peptide negative or CpN-Nc). Five women with secondary amenorrhoea were C-peptide positive or CpP-Am and the other six were C-peptide negative or CpN-Am.