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The effect of oral contraception on macroprolactin levels in women with macroprolactinemia: A pilot study

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ABSTRACT

Background: Despite a high prevalence of macroprolactinemia in the population, the only drugs found to change macroprolactin (big-big prolactin) levels were dopamine receptor agonists.
Methods: The aim of this study was to investigate the effect of oral contraceptive pills containing ethinyl estradiol and levonorgestrel on serum macroprolactin levels in patients with macroprolactinemia. The study population included 21 premenopausal women with isolated macroprolactinemia, 11 of whom were treated with oral contraceptive pills. Serum prolactin and macroprolactin levels were assessed at baseline and after 16 weeks of treatment.
Results: Oral contraceptive pills administered for 16 weeks slightly increased pre-polyethylene glycol serum prolactin levels and macroprolactin levels and the effect of this treatment correlated with their baseline values.
Conclusions: Our results suggest that oral contraceptive pills containing ethinyl estradiol and levonorgestrel exhibit a stimulatory effect on macroprolactin production in women with basically high macroprolactin levels.

Introduction

The monomeric form of prolactin has a molecular weight of 23 kDa and is known to be both biologically and immunologically active, accounting for most of the total prolactin immunoreactivity in the serum [1,2]. In addition, there are two other prolactin isoforms that display higher molecular weights, referred to as big prolactin (45–50 kDa) and big-big prolactin also known as macroprolactin (150–170 kDa) [3,4]. Macroprolactin consists mainly of complexes of prolactin and IgG, but complexes of prolactin with IgA or IgM, or aggregates of covalent or noncovalent polymers of monomeric prolactin, some extensively glycosylated, may also occur [5,6]. Macroprolactin has substantially longer renal clearance than monomeric prolactin resulting in its accumulation in the serum [1,7].

Because of its large size, macroprolactin is thought to be confined to the vasculature with limited bioavailability to prolactin receptors [1]. Macroprolactinemia is a frequent cause of misdiagnosis and mismanagement of patients with elevated prolactin levels [7]. Although biological activity has been demonstrated *in vitro*, some authors claim that macroprolactin lacks biological activity *in vivo* because it cannot cross the endothelial lining and reach the cell surface receptors [8].

The term "macroprolactinemia" is typically applied to cases where concentration of macroprolactin exceeds 60% of total serum prolactin concentration [9]. Depending on the immunoassay used, the prevalence of macroprolactinemia in hyperprolactinemic patients ranges between 15 and 46% [10]. Because of its high prevalence in the female population and a possible association with menstrual disturbances [7], many young women with this condition probably receive estrogen and progestin preparations. The aim of this study was to investigate the effect of oral contraceptive pills on serum macroprolactin levels in patients with macroprolactinemia.

Materials and methods

The study was carried out in accordance with the principles of the Declaration of Helsinki. All patients gave written, informed consent, and the local ethics committee approved the study protocol. The study population consisted of 11 asymptomatic women (20–40 years old) with macroprolactinemia, defined as the

Abbreviations: FSH, follicle-stimulating hormone; Ig, immunoglobulin; LH, luteinizing hormone; TSH, thyroid stimulating hormone; SD, standard deviation.

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prolactin recovery less than 40% and post-polyethylene glycol serum prolactin levels less than 20 ng/mL, planning to take oral contraceptive pills containing 30 μg of ethinyl estradiol and 150 μg of levonorgestrel. These patients were compared with the control group including 10 age- and weight- matched women with macroprolactinemia not receiving any treatment. We excluded patients with coexisting prolactinomas or other pituitary tumors, impaired renal or hepatic function, thyroid disorders, polycystic ovary syndrome, diabetes, pregnancy or lactation, as well as patients treated with drugs known either to affect plasma prolactin levels or to interact with oral contraceptive pills.

All blood samples were taken between 8.00 and 9.00 a.m. after a 12-hr overnight fast in a quiet, temperature-controlled room (24–25 °C) before and after 16 weeks of treatment. All the tests were carried out by a person blinded to individuals' identity and all clinical details. Serum prolactin levels were determined before and shortly after polyethylene glycol precipitation by the enzyme-linked immunosorbent assay (DRG Instruments GmbH, Marburg, Germany). The assay had a lower limit of sensitivity of 0.35 ng/mL. The intra- and inter-assay coefficients of variations were 4.3% and 6.0%, respectively. To perform polyethylene glycol precipitation, 250 μL of sera was mixed with an equal volume of 25% cold polyethylene glycol 6000 dissolved in phosphate buffered saline (Sigma, 137 mmol/L sodium chloride, 10 mmol/L sodium phosphate, pH = 7.4) and incubated for 10 min at room temperature. After vortex mixing for 30 s, the suspension was clarified by centrifugation at 3000 for 30 min, before prolactin measurement. To correct for the dilution with polyethylene glycol, the post-polyethylene glycol prolactin concentration was determined by multiplying the prolactin result by 2. Prolactin recovery was diagnosed using the following formula: serum prolactin after polyethylene glycol precipitation/serum prolactin before polyethylene glycol precipitation × 100. Macroprolactinemia was diagnosed if the prolactin recovery was less than 40%. Serum levels of TSH, total and free thyroxine and triiodothyronine were measured using an electrochemiluminescence immunoassay method (Roche Diagnostics, Lewes, UK). Serum levels of creatinine were assayed by routine laboratory techniques. The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation.

The Kolmogorov-Smirnov test was used as the first statistical analysis approach to verify data distribution normality. Because of skewed distributions, values for prolactin, prolactin recovery, TSH and free thyroid hormones were natural-log transformed to meet the assumptions of parametric tests. Both groups were compared by *t*-tests for independent samples. The differences between the means of variables within the same treatment group were analyzed with Student's paired *t*-test. For categorical variables, chi^2 test was used. Correlations were calculated using Kendall's tau test. Statistical significance was defined as p less than 0.05.

Results

Baseline serum levels of all investigated parameters were similar in both groups of patients (Table 1). Oral contraceptive pills were well tolerated and all patients completed the study period. No changes in serum pre- and post-polyethylene glycol levels, macroprolactin, as well as in serum levels of TSH, free thyroxine and triiodothyronine were observed in untreated patients with macroprolactinemia. Oral contraceptive pills administered for 16 weeks increased pre-polyethylene glycol serum prolactin levels and macroprolactin content. However, they did not affect post-polyethylene glycol serum prolactin levels, serum TSH, free thyroxine and triiodothyronine levels as well as the estimated glomerular filtration rate. At the end of the treatment period, total serum prolactin levels and macroprolactin content were still different from those observed in the control subjects (Table 2).

Table 1
Baseline characteristics of patients.

	Oral contraceptive pills	No treatment
Number of patients	11	10
Age [years]	29 (3)	30 (4)
Smokers [%]	27	30
Body mass index [kg/m^2]	25.9 (2.1)	26.2 (2.3)
Prolactin before polyethylene glycol precipitation [ng/mL]	68 (10)	60 (14)
Prolactin after polyethylene glycol precipitation [ng/mL]	12 (3)	10 (4)
Macroprolactin [%][a]	82 (5)	83 (6)
TSH [mIU/L]	1.3 (0.6)	1.2 (0.5)
Free thyroxine [pmol/L]	17.2 (2.0)	16.8 (1.9)
Free triiodothyronine [pmol/L]	4.2 (0.7)	4.0 (0.6)
Estimated glomerular filtration rate [mL/min]	92 (10)	90 (8)

[a] [1 − (serum prolactin after polyethylene glycol precipitation/serum prolactin before polyethylene glycol precipitation)] × 100.
Data represent the mean (SD).

At entry, there was a strong correlation between total prolactin levels and macroprolactin content ($r = 0.74$, $p < 0.001$). The effect of the treatment on total prolactin levels and macroprolactin content correlated with their baseline values (total prolactin: $r = 0.49$, $p < 0.001$; macroprolactin: $r = 0.53$, $p < 0.001$). Moreover, an increase in macroprolactin content correlated with the effect of oral contraceptive pills on pre-polyethylene glycol prolactin levels ($r = 0.69$, $p < 0.001$). No other correlations were found in both baseline conditions and after treatment.

Discussion

In this study, we have found for the first time that oral contraceptive pills slightly increased macroprolactin levels in

Table 2
The effect of oral contraceptive pills on serum levels of the investigated parameters in patients with macroprolactinemia.

	Oral contraceptive pills Mean (SD) [Δ%]	No treatment Mean (SD) [Δ%]
Prolactin before polyethylene glycol precipitation [ng/mL]		
Baseline value	68 (10)	60 (14)
After 16 weeks of treatment	79 (11) [16][a,b]	64 (11) [7]
Prolactin after polyethylene glycol precipitation [ng/mL]		
Baseline value	12 (3)	10 (4)
After 16 weeks of treatment	10 (4) [−17]	12 (4) [20]
Macroprolactin [%][d]		
Baseline value	82 (5)	83 (6)
After 16 weeks of treatment	87 (5) [6][a,b,c]	81 (5) [−2]
TSH [mIU/L]		
Baseline value	1.3 (0.6)	1.2 (0.5)
After 16 weeks of treatment	1.5 (0.7) [15]	1.3 (0.6) [8]
Free thyroxine [pmol/L]		
Baseline value	17.2 (2.0)	16.8 (1.9)
After 16 weeks of treatment	16.7 (2.3) [−3]	17.0 (2.4) [1]
Free triiodothyronine [pmol/L]		
Baseline value	4.2 (0.7)	4.0 (0.6)
After 16 weeks of treatment	3.7 (0.7) [−12]	4.2 (0.8) [5]
Estimated glomerular filtration rate [mL/min]		
Baseline value	92 (10)	90 (8)
After 16 weeks of treatment	90 (10) [−2]	94 (11) [4]

[a] $p < 0.05$ *vs.* baseline value.
[b] $p < 0.01$ *vs.* control subjects.
[c] Macroprolactin levels increased in eight women treated with oral contraceptive pills, while in two patients receiving ethinyl estradiol and levonorgestrel as well as in all control subjects remained at the similar levels throughout the study.
[d] [1 − (serum prolactin after polyethylene glycol precipitation/serum prolactin before polyethylene glycol precipitation)] × 100.