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The impact of GnRH agonists in patients with endometriosis on prolactin and sex hormone levels: a pilot study

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ABSTRACT

Objective: Gonadotropin releasing hormone agonists (GnRHa) decrease the expression of growth factors involved in the development of human endometriotic tissue. As endometriosis has been found to be associated with a mild increase in prolactin (PRL) serum levels, we aimed to evaluate changes in PRL serum levels as well as other hormones relevant to endometriosis and infertility during long-term administration of GnRHas in women with endometriosis.
Study design: In this prospective pilot study we obtained blood samples on the first day of leuporeline administration and then subsequently after 4, 8 and 12 weeks in 22 patients.
Results: Median PRL levels were unchanged after 4 weeks, but significantly decreased 8 and 12 weeks after the first leuporeline administration ($p_1 = 0.085$, $p_2 = 0.020$, $p_3 = 0.001$). There was no significant decrease in serum anti-Mullerian hormone (AMH) levels over the whole period of down regulation with leuporeline ($p_{1-3} > 0.05$).
Conclusion: Our data support the hypothesis that the decrease of PRL levels might contribute to the known effect of GnRH treatment in patients with endometriosis via suppression of VEGF expression in endometriotic lesions. Moreover this study lends support to the thesis that AMH remains stable under GnRHa therapy and therefore can be also used as a marker of ovarian function prior to IVF-stimulation during down regulation.

Introduction

Endometriosis represents a chronic estrogen dependent disease, which can be asymptomatic or result in symptoms such as pelvic pain, dysmenorrhea, dyspareunia and infertility. Although the exact mechanisms leading to infertility are still unknown, it is hypothesized that an overproduction of prostaglandins, cytokines and chemokines result in an inflammatory process that impairs ovarian, tubal and endometrial function [1–4].

Gonadotropin releasing hormone agonists (GnRHa) represent a common treatment option for women with endometriosis and moderate to severe pelvic pain. Continuous administration of GnRHa result in a hypoestrogenic state due to suppression of the hypothalamic–ovarian axis and ovarian steroidogenesis. In women with infertility related to endometriosis, long-term-administration of GnRHa for a period of 3–6 months prior to in vitro fertilization (IVF) or intracytoplasmatic sperm injection (ICSI) increases the chance of clinical pregnancy by fourfold [5,6]. GnRHa seem to have direct effects on the endometrium via GnRH receptors present in endometrial cells [7]. Furthermore they decrease the expression of growth factors involved in the development of human endometriotic tissue, such as the vascular endothelial growth factor (VEGF) and minimize macrophage infiltration and microvessel density of endometriotic lesions [6,8].

Endometriosis has been found to be associated with a mild increase in prolactin (PRL) serum levels [9]. Bilibio et al. [10] recently demonstrated the presence of dopamine D2 receptor polymorphism in patients with endometriosis, which could be responsible for the rise in serum PRL levels due to a defect in post-receptor signaling mechanisms. The significance of these findings is not fully understood, but the powerful induction of angiogenesis via PRL could be involved in the implantation and maintenance of

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endometriotic lesions [11,12]. Thus, the reduction of endometriosis symptoms with the use of dopamine agonists might be explained through inhibition of prolactin mediated angiogenetic effects [10–13].

To the best of our knowledge the effect of long-term GnRHa administration on PRL serum levels in women with endometriosis has not yet been studied. Therefore the aim of this study was to evaluate changes in PRL serum levels as well as other hormones relevant to endometriosis and infertility during long-term administration of GnRHas in women with endometriosis prior to in vitro fertilization.

Materials and methods

Study population and study design

The present study was conducted as a prospective pilot study in women with infertility and endometriosis. Long-term GnRHa administration prior to in vitro fertilization increases clinical pregnancy rate and live birth rate in women with endometriosis and is therefore standard of care at our department [5]. Depot-leuproreline (Enantone-Gyn®, containing 3.75 mg leuproreline-acetate, equivalent 3.57 mg leuproreline) is administered subcutaneously every 4 weeks for 3 months. No hormonal add-back therapy is used.

All patients with histologically verified endometriosis that had undergone diagnostic or therapeutic laparoscopy for infertility from January 2012 to December 2013, and received long-term-administration of GnRHas prior to in vitro fertilization were invited to participate in this study. Patients were excluded if hyperandrogenemia (due to polycystic ovary syndrome or other reasons) was present, in case of untreated hyper- or hypothyroidism, or previous GnRHa application.

The primary endpoint of the study was to evaluate changes in PRL levels during the therapy with GnRHas. Secondary endpoints were changes in anti-Mullerian-hormone (AMH) and sexual hormone levels, including estrogen, progesterone, testosterone, androstenedione, luteinizing hormone, follicle stimulating hormone as well as thyroid stimulating hormone. The study was approved by the Institutional Review Board of the Medical University of Vienna (IRB number: 1003/312). Written informed consent was obtained from all patients.

Blood sampling protocol and laboratory determinations

A total of four blood samples were obtained from each patient. The first sample was obtained on the first day of leuproreline administration. The subsequent samples were obtained after 4, 8 and 12 weeks of leuproreline administration.

All examined serum parameters were determined in the ISO-certified central laboratory of the General Hospital of Vienna, Vienna, Austria using commercially available assays. Radioimmunoassays were used to determine serum levels of luteinizing hormone (LH; Autodelfia; Wallac Oy, Turku, Finland), follicle stimulating hormone (FSH; Enzymun ES700; Böhringer Mannheim, Mannheim, Germany), estrogen (E2; electrochemiluminescence immunoassay "ECLIA"; Cobas®, Roche Diagnostics GmbH, Mannheim, Germany), progesterone (Coat-ACoat RIA; DPC, Los Angeles, CA, USA), testosterone (Immunotech, Westbrook, ME, USA), androstenedione (Immunotech, Westbrook, ME, USA), and anti-Mullerian-hormone (AMH; DSL Active MIS/AMH assay; Beckman Coulter Inc., Brea, USA), prolactin (PRL; electrochemiluminescence immunoassay "ECLIA"; Cobas®, Roche Diagnostics GmbH, Mannheim, Germany), thyroid stimulating hormone (TSH; electrochemiluminescence immunoassay "ECLIA"; Cobas®, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Values are given as median (inter-quartile range [IQR]). To compare groups, chi-square tests and Kruskal–Wallis-tests were used. Differences were considered statistically significant if $p < 0.05$. Statistical analysis was performed using SPSS 15.0.1 for Windows (SPSS Inc., 1989–2006).

Results

A total of 22 patients were included in this study. Basic patient characteristics are provided in Table 1. Median age was 30.0 years [IQR 27.0–35.3]. All patients revealed a revised American Fertility Society (rAFS) classification stage of 2 or higher. All women completed the 3 months of depot-leuproreline administration as well as all study visits. There were no adverse events related to the use of depot-leuproreline. The course of serum hormone levels is provided in Table 2. Median PRL levels were unchanged after 4 weeks, but significantly decreased 8 and 12 weeks after the first leuproreline administration (Fig. 1).

Estrogen levels at 4, 8 and 12 weeks after leuproreline administration decreased significantly from 120 to 10 pg/ml ($p_{1-3} = 0.000$). Testosterone levels decreased significantly after 12 weeks of leuproreline from 0.18 to 0.16 ng/ml ($p_3 = 0.005$). As expected, there was a significant decrease of LH at 4, 8 and 12 weeks after the first leuproreline administration. There were no significant changes in TSH and androstenedione levels during down regulation.

There was no significant decrease in serum AMH-levels or FSH levels over the whole period of down regulation with leuproreline (Fig. 1).

Comment

In this study we observed a significant decrease of PRL serum levels in women with endometriosis treated with GnRHa, while AMH remained stable over the 12-week treatment period.

Prolactin represents a powerful inducer of angiogenesis and several studies found a mild rise of PRL serum levels in women with endometriosis [10,14,15]. The angiogenic effect of PRL has been postulated to play a role in the implantation process of ectopic endometriosis tissue. Prolactin has also been proposed as a serum marker for endometriosis in combination with CA 12-5

Table 1
Basic patient characteristics.

Age (years)	30.0 [27.0–35.3]
BMI (kg/m^2)	22.7 [20.6–28.4]
Primary infertility (*n*, %)	16 (72.7)
Secondary infertility (*n*, %)	6 (27.3)
Pregnancies (*n*, %)	
1	4 (18.2)
2	2 (9.1)
>2	0
Parity (*n*, %)	
1	3 (13.6)
2	0
Dysmenorrhea (*n*, %)	19 (86.4)
None	3 (13.6)
Mild	0
Moderate	10 (45.5)
Severe	9 (40.9)
RAFS (*n*, %)	
Stage I	0
Stage II	3 (13.6)
Stage III	7 (31.8)
Stage IV	12 (54.5)

Note: Value expressed as either median with inter-quartile range [IQR] or as *n* (%).