

HYPERPROLACTINAEMIA AS A POTENTIAL CAUSE OF INFERTILITY

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Summary: Establishing of hormonal disturbances is one of the most important steps in infertility studies. The aim of the study was to evaluate the importance, frequency and treatment efficiency of hyperprolactinaemia in infertile patients. Eighty seven infertile patients have been examined in this study. Matched samples of peripheral blood were taken for hormonal analyses in the early follicular, periovulatory and midluteal phases of the cycle. Between the 4th and 7th day of the cycle ultrasonographic and haemodynamic examinations have been carried out at the ovarian and uterine levels. Hyperprolactinaemia was detected in 25 women, in which prolactin levels ranged 628.4–8000 mIU/L. We started dopamine agonists (bromocriptine/cabergoline) treatment individually dosaged. Menstrual cycle as well as prolactin levels restored in all patients 3 months after treatment initiation. Hyperprolactinaemia can derange fertility potential, so its early and precise detection and adequate therapy are essential for restoration of regular menstrual cycle and successful infertility treatment.

Key words: hyperprolactinemia, infertility, treatment

Introduction

Precise development of the reproductive process in women, being in mutual interaction, is under subtle regulative mechanisms control, which unite harmonious function of the central nervous system, hypothalamus, hypophysis and ovary, as a key reproductive organ with its own auto-regulative mechanism of action. Even a minor disorder in any phase of this complex system function provokes neuroimmune-endocrine dysbalance with development of appropriate diseases (1–3).

Precise and dynamic examination of hormonal status in various phases of menstrual cycle is of great importance for a proper recognition of pathophysiological mechanisms in occurrence of a specific disease and decision for an adequate treatment according to the individual response (4).

Hyperprolactinemia (plasma concentration of

prolactin >20 µg/L; >580 mIU/L) is one of the most frequent endocrine causes of infertility. Hyperprolactinaemia occurs in 15–20% cases of women with chronic anovulatory cycles. Therefore, diagnosis and correction of this neuroendocrine dysbalance are important in the early stage of examination and treatment of infertility – an important vital and medical problem.

Secretion of prolactin (PRL) is under control of numerous neuroendocrine mediators, which in stimulative (thyroid releasing hormone-TRH, endogenous opiates, serotonin, cholecystokinin, vasointestinal peptide, angiotensin II, vasotocin, steroid hormones-estrogens) or inhibition sense (dopamine, gastrin, neurotensine, bradykinin, gamma-aminobutyric acid-GABA) influence the PRL production. Dopamine is the main prolactin-inhibiting factor, and dopamine receptors (D₂, D₁) have been discovered on lactotrophs (cells in the anterior pituitary lobe which secrete prolactin (5–7)).

Causes of hyperprolactinaemia may be pathological, functional and pharmacological. Pituitary adenomas – prolactinomas, in particular microprolactinomas, are the most frequent pathological-organic causes of hyperprolactinaemia. Microprolactinomas (prolactinomas smaller than 1 cm in diameter) can be diagnosed by targeted computerized tomography (CT scan) or nuclear magnetic resonance (NMR) examina-

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tion of cellular region, as well as by appropriate dynamic stimulative and suppressive tests for examination of prolactin secretion (8-10).

The aim of the study was to evaluate the importance, frequency and treatment efficiency of hyperprolactinaemia in infertile patients.

Material and Methods

Eighty seven infertile patients have been examined in this study. Matched samples of peripheral blood were taken for hormonal analyses (Follicle Stimulating Hormone, FSH; Luteinizing Hormone, LH; aestradiol, E₂; progesterone, Pg and prolactin, PRL, 3 times every 20 minutes) in the early follicular, periovulatory and midluteal phase of the cycle.

Plasma hormones (FSH, LH, aestradiol, progesterone and prolactin) were determined by MEIA method using ABBOTT reagents on AXYM. Microparticle enzyme immunoassay (MEIA) technology uses a solution of suspended, submicron sized latex particles to measure analytes. The particles are coated with a capture molecule specific for the analyte being measured. The effective surface area of microparticles increases assay kinetics and decreases assay incubation time. This permits MEIA assay to be completed in a shorter time than other immunoassays. Normal range for prolactin level is between 33.3-580.8 mIU/L.

Between the 4th and 7th day of the cycle the ordinary ultrasonographic and haemodynamic examinations by means of Color Doppler Ultrasonography (Aloca SSD 2000, vaginal probe-5MHz) have been carried out at the ovarian and uterine levels.

The time period of individually used therapy (dopamine agonists: bromocriptine/cabergoline) in hyperprolactinaemic patients ranged from 3-12 months and over that period PRL levels as well as restoration of menstrual cycle was evaluated. The daily dose and the total received dose of medicine (bromocriptine) was calculated. The efficiency of therapy was estimated according to dose and duration of therapy.

The following statistical methods were used: one-Simple Kolmogorov-Smirnov test (for distribution testing), Wilcoxon's test (for testing of depending non-parametrical samples), and Person's and Spearman's correlation (for testing of correlative association of the monitored variables) (4).

Results

Hyperprolactinaemia was detected in 25 women and this group has been monitored. We found transitory hyperprolactinaemia only in periovulatory phase in 4/25 patients and hyperprolactinaemia only in midluteal phase in 6/25 patients. Only three cycles were ovulatory proved by hormonal, ultrasonographic and

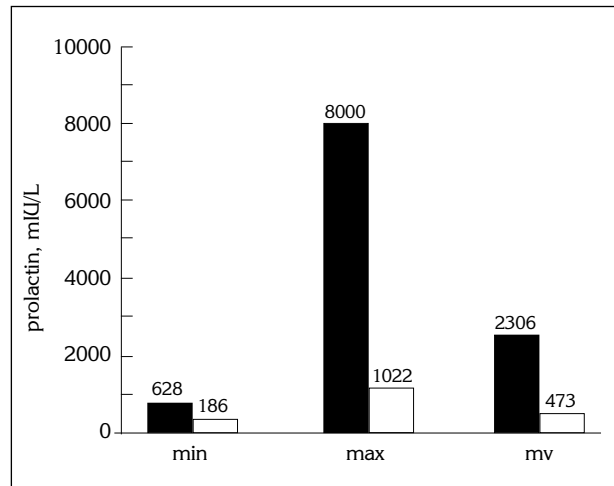


Figure 1. Bar chart showing minimal (min), maximal (max) and mean values (mv) of prolactin levels before (■) and after (□) used bromocriptine therapy

haemodynamic parameters, but in cases of mild hyperprolactinaemia. Six patients were with amenorrhoea and 12 were with oligomenorrhoea. Presence of microprolactinoma was detected in 2 cases.

We started dopamine agonist treatment individually dosaged (bromocriptine: 2.5-15 mg daily for 3-12 months; or cabergoline in 5/25 patients: 0.25-0.5 mg twice a week for the same period).

Value of prolactin before starting with the therapy ranged from minimum 628.4 mIU/L to maximum 8000 mIU/L with a mean value of prolactin in the monitored group from 2306.9 ± 1908.5 mIU/L (MV \pm SD). Prolactin value after the applied therapy ranged from 186.0 mIU/L to maximum 1022.0 mIU/L with a mean value of 473.3 ± 217.9 mIU/L (Figure 1). In 77% of patients after the therapy, a normalization of prolactin value occurred, and disappearance of microprolactinoma was established during NMR examination.

A statistically important positive correlation ($p < 0.05$) of prolactin value prior to beginning of treatment and duration of therapy had been noticed as well as a high statistically important correlation ($p < 0.01$) of prolactin value prior to therapy and the completely received medicine dose during the therapy.

The time period of therapy ranged from 3-12 months, with a mean value of 5.3 ± 3.2 months. In that period pregnancy was established in 12 patients (in 6 cases medications for ovulation induction were given). Menstrual cycle as well as PRL levels restored in all patients 3 months after treatment initiation.

The daily dose of the bromocriptine ranged from 5-15 mg with a mean value of 7.5 ± 3.5 mg. The total received dose of medicine during the therapy ranged from 150 mg to maximum 4125 mg with a mean value of 1294.3 ± 1114.3 mg. A high statisti-

cally important decrease in prolactin value ($p < 0.01$) occurred after the therapy.

There is a negative correlation of prolactin value after the treatment with the duration of therapy as well as with a total daily dose of medicine and the total received dose of medicine during the therapy however without a statistical importance. Negative correlation indicates that the longer the therapy the prolactin value at the end of therapy was lower; the greater the daily dose the greater fall of prolactin, and the greater totally used dose during the therapy the greater fall of PRL.

Discussion

According to many clinical and experimental researches, there are several hypothetical models in explanation of aetiology of hyperprolactinaemia (with or without presence of prolactinomas): reduction of inhibitory hypothalamic (dopaminergic) tonus, reduction of pituitary dopamine receptors, lack of intracellular inhibitory messenger system (post-receptor defect), and vascular anomalies or membrane defect of adenoma (4).

The most frequent symptoms and signs caused by increased secretion of prolactin, a hormone that in physiologic conditions controls lactation and inhibits the gonadotrophin effect in women, are: a disorder of menstrual cycle (anovulatory cycles, secondary amenorrhea, oligomenorrhea, dysmenorrhea, polymenorrhea) hyperprolactinaemia registered in 15–20% of cases; galactorrhea (can be, but has not to be, associated with hyperprolactinaemia, depending on concentration and sensitivity of PRL receptors in the breast being affected by steroid hormones) hyperprolactinaemia registered in 30–80% of cases; infertility hyperprolactinaemia registered in 20–30% of infertile patients, and slowed-down or postponed puberty (primary amenorrhea) (11, 12).

Hyperprolactinaemia inhibits follicle growth and maturation and steroidogenesis at several levels:

1. Via a hypothalamus level, suppressing together with a consequent increased secretion of dopamine, secretion of gonadotrophin releasing hormone (GnRH);
2. At the ovarian level directly interfering with LH induced steroidogenesis and production of androgen in theca cells of internal follicle;
3. In the follicle granulosa cells suppressing synthesis of oestrogen by inhibiting FSH induced aromatase enzyme activities. Hypoestrogenaemia causes a reduced mitosis and differentiation of follicle granulosa cells as well as reduction of steroidogenesis potential in corpus luteum due to inadequate prepared follicle (13).

There are cases of idiopathic infertility with transitory pre-ovulation increase in prolactin secretion, which can have a negative impact on fertilization, implantation, embryogenesis and corpus luteum function (14).

The treatment of hyperprolactinaemia is directed towards elimination of the cause of increased prolactin secretion – no more taking of certain medicine, correction of metabolic-endocrine state, or elimination of prolactinoma (15).

In the therapy of both functional and pathological hyperprolactinaemia caused by microprolactinoma, dopamine agonists from ergot derivatives have been indicated and effectively used, from which the most important are: bromocriptine, lisuride and cabergoline. Cabergoline belongs to dopaminergic ergoline preparations with prolonged normoprolactinaemic effect and more superior characteristics in comparison to most dopamine agonists with respect to establishing regular ovarian cycles, reduction of adenoma, establishing of fertility and better toleration (10, 16, 17).

Our findings agree with the results of other authors that early and prompt diagnosis of hyperprolactinaemia at the beginning of infertility examination as well as adequate and individualized dose and route of therapy (primarily with dopamine agonists) are successful in solving infertility problem in most of the cases (18–22).

In conclusion, the obtained data in this study indicate the necessity of: determining the initial dose of bromocriptine vis-a-vis prolactin values, with individual adjustment of the dose until the optimal dose has been reached; and control of prolactin value during the therapy with gradual diminishing of the daily dose of medicine in compliance with the fall of prolactin value to the maintenance dose or even a complete (gradual) cancellation of the therapy.

For an adequate follicle growth and maturation, fertilisation and implantation a balanced and timely synchronized production of hormones as well as paracrine ovarian and uterine factors are necessary. Hyperprolactinaemia can derange fertility potency, so its early detection and adequate treatment are essential for restoration of the menstrual cycle, better control of ovarian response during ovarian stimulation procedure and successful infertility management.

In future studies it is interesting to see how long the normal values of prolactin after stopping the therapy can be maintained and whether there is a connection with its initial values, duration of therapy and type and dose of the regimen.

HIPERPROLAKTINEMIJA KAO POTENCIJALNI UZROK INFERTILITETA

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Kratak sadržaj: Istraživanje hormonskih poremećaja je jedan od najvažnijih koraka u ispitivanju infertiliteta. Cilj ove studije je bio da se proceni značaj, učestalost i efikasnost lečenja stanja hiperprolaktinemije kod infertilnih pacijentkinja. Osamdeset sedam pacijentkinja je bilo ispitano u ovoj studiji. Odgovarajući uzorci periferne krvi su uzimani za hormonske analize u ranoj folikularnoj, periovulatornoj i midlutealnoj fazi ciklusa. Između 4. i 7. dana ciklusa ultrasonografska i hemodinamska ispitivanja su sprovedena na ovarijalnom i uterusnom nivou. Hiperprolaktinemija je detektovana kod 25 žena, kod kojih je nivo prolaktina bio između 628.4 8000 mIU/L. Započeta je terapija dopaminskim agonistima (bromokriptin/kabergolin), individualno dozirana. Menstrualna cikličnost, kao i nivoi prolaktina su se normalizovali kod svih pacijentkinja 3 meseca od početka terapije. Hiperprolaktinemija može da poremeti fertilni potencijal, te je njegova rana i precizna detekcija i adekvatna terapija veoma važna za uspostavljanje regularne menstrualne cikličnosti i uspešan tretman infertiliteta.

Ključne reči: hiperprolaktinemija, infertilitet, lečenje

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