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Original Article

ASSOCIATION BETWEEN HYPERPROLACTINAEMIA AND OTHER CAUSES OF FEMALE INFERTILITY

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Abstract. *Hyperprolactinaemia is one of the major causes of reproductive axis disorders. Adequate treatment for hyperprolactinaemia is very successful in restoring ovulation, but there is still a proportion of patients unable to achieve pregnancy despite adequate control of hyperprolactinaemia. This prospective clinical trial included 104 hyperprolactinaemic patients in reproductive age: 78/104 (75%) suffered from infertility and the other 26 hyperprolactinaemic patients were still unmarried and not interested in pregnancy. Hyperpolactinaemia as the only reason for anovulation and infertility was diagnosed in 43/78 (55.12%) of our patients. In 35/78 (44.88%) patients, hyperprolactinaemia was associated with other causes of infertility: endometriosis, premature ovarian failure, PCO and insulin resistance, etc. After the appropriate treatment, mostly with bromocriptine (in 69/78 – 88.46%, alone or in combination with induction of ovulation), 35/78 (44.87%) patients achieved pregnancy. In the group of infertile patients with hyperolactinaemia as the only cause of infertility, 33/43 (76.74%) patients became pregnant, and in the group of patients who had combination of hyperprolactinaemia and other causes of infertility only 2/35 (5.71%) achieved pregnancy. The treatment of hyperprolactinaemia is obligatory in all patients with infertility. If adequate suppression of serum prolactin levels is achieved, but the pregnancy is still missing despite the fact that ovulatory cycles are established, the other causes of infertility should be searched for, and the clinician should not reject the possible existence of some unknown cause of infertility, so the patient should be referred to ART procedures which give more chances in such circumstances.*

Key words: *Hyperprolactinaemia, infertility, bromocriptine, assisted reproductive techniques*

Introduction

Hyperprolactinaemia is one of the major causes of reproductive axis disorders, being the major cause of hypogonadotropic anovulation and is one of the leading causes of infertility in women aged 25–34 [1–4]. Adequate treatment for hyperprolactinaemia is very successful in restoring ovulation. Nevertheless there is still a proportion of patients unable to achieve pregnancy despite adequate control of hyperpolactinaemia.

The aim of this article is to present the association between hyperprolactinaemia and other causes of female infertility, the combination which could be resistant to infertility treatment.

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Material and Methods

This prospective clinical trial included 104 hyperprolactinaemic patients in reproductive age. The diagnosis of hyperprolactinaemia was established by single measurements of serum prolactine levels in two separate occasions (at least two hours before or after sleeping). The serum was obtained without excessive venipuncture stress and a level higher than upper limit confirmed the diagnosis (> 530 mIU/l according to World Health Organization Standard 84/500), as it was previously described [3, 5, 6].

All hyperprolactinaemic patients referred to our Clinic were subjects of clinical investigation: anamnesis, clinical exam, pelvic ultrasound examination, urine and blood analyses (blood picture, biochemical parameters including parameters of hepatic and renal function, hormonal analysis). The patients with secondary hyperprolactinaemia (due to medicaments, hypothyreosis, renal or hepatic failure, etc.) were excluded from further investigation. The other 104 hyperprolactinaemic patients were included in this investigation. Transvaginal ultrasound (TVUS) measurements of follicle diameters were performed during menstrual cycle in patients with regular cycles. At day 2–4 of spontaneous menstrual cycle serum levels of follicle-stimulating hormone

(FSH), luteinizing hormone (LH), prolactin (PRL), oestradiol (Es), progesterone (Pr) and testosterone (Ts) were measured and in the middle of luteal phase (day 22) serum levels of Pr and PRL were measured as well. Ovulation was confirmed by adequate development of dominate follicle, appearance of corpus luteum on TVUS examination and serum progesterone levels > 5 ng/ml (16 nmol/l) in the middle of luteal phase (day 22), as it was described previously [7, 8]. Pituitary MR was performed in all hyperprolactinaemic patients with serum prolactin levels higher than 2000 mIU/l, as well in cases with disproportion of serum prolactin level and severity of clinical findings (e.g. prolactin < 2000 mIU/l and long lasting amenorrhoea). In patients with headaches and visual disturbances pituitary MR was also performed. Visus, perimetria and examination of *fundus oculi* were performed in patients with microprolatinomas and headaches.

Infertile patients were also subjects of infertility investigation: hysterosalpingography or sonohysterosalpyngography, analysis for related infections, laparoscopy and hysteroscopy where indicated, etc. Husband's semen analyses were performed too. The effects of therapy for hyperprolactinaemia were evaluated at first checkup, at the 45th day of the therapy and after 3, 6 and 12 months of therapy. If the pregnancy was missing after 6–9 months from the beginning of the therapy for hyperprolactinaemia and normalization of serum prolactin levels, induction of ovulation was started parallel with therapy for hyperprolactinaemia or patient was referred to ART (assisted reproductive technology) procedures (which had been already done in infertile couples with mechanical infertility or male factor and other indications for ART). Patients who achieved pregnancy were controlled and delivered at our Clinic.

Data were processed and statistical analyses were performed using commercial software. Statistical significance was tested with Student's t-test ($p<0.05$ was considered as statistically significant) and t-test for proportions for small independent samples with Cochran and Cox's corrective approximate method for small independent samples was performed where needed.

Results

Clinical characteristics of all patients included in this prospective clinical investigation are shown in Table 1.

Clinical characteristics of infertile hyperprolactinaemic patients (78/104 or 75%) are shown in Table 2. The other 26 hyperprolactinaemic patients were still unmarried and not interested in pregnancy, referred to our Clinic due to cycle irregularity, galactorrhoea or alopecia and hirsutism.

Serum prolactin levels were higher in amenorrhoeic infertile patients in comparison with serum prolactin levels in patients with oligomenorrhoea (1489.44± 388.19 mIU/l; p=0.025463). There were no significant differences regarding age and duration of infertility between hyperolactinaemic infertile patients with amenorrhoea, oligomenorrhoea and regular cycles, with exception of statistically significant younger age of oligomenorrhoeic patients in comparison with age of the patients with normal cycles (Table 3 and 4).

Table 1. Clinical characteristics of all hyperprolactinaemic patients (n=104).

Age (years)		29.96 ± 5.81
Cycle irregularity	60/104	(57.69%)
– amenorrhoea	30/104	(28.84%)
– oligomenorrhoea	30/104	(28.84%)
Regular cycle	44/104	(42.31%)
Galactorrhoea	12/104	(11.53%)
Infertility	78/104	(75.00%)
Hirsutism	13/104	(12.50%)
Alopecia	6/104	(5.76%)
Premature ovarian failure	3/104	(2.88%)
Macroprolactinoma	1/104	(0.96%)
Microprolactinoma	11/104	(10.57%)
Enlargement of sella turcica	1/104	(0.96%)
Anovulatory cycles	76/104	(73.07%)
Ovulatory cycles	28/104	(26.93%)
– inadequate luteal phase		11/28 (39.29%) or 11/104 (10.57%)
– adequate luteal phase		17/28 (60.71%) or 17/104 (16.35%)

Table 2. Clinical characteristics of hyperprolactinaemic patients with infertility (n=78)

Age (years)		30.55 ± 5.22
Duration of infertility (years)		4.56 ± 2.86
Primary infertility	67/78	(85.89%)
Secondary infertility	11/78	(14.11%)
Amenorrhoea	21/78	(26.92%)
Oligomenorrhoea	30/78	(38.46%)
Regular cycles	27/78	(34.61%)
Galactorrhoea	8/78	(10.25%)

Table 3. Age of hyperolactinaemic patients with infertility

	1. Patients with amenorrhoea n=21	2. Patients with oligomenorrhoea n=30	3. Patients with regular cycles n=27
Age (years) X ± SD	32.0 ± 5.61	28.06 ± 3.61	31.83 ± 3.79

t-test for 1 and 2 p=0.052944; t-test for 1 and 3 p=0.924765; t-test for 2 and 3 p=0.04001

Table 4. Duration of infertility in patients with hyperprolactinaemia

	1. Patients with amenorrhoea n=21	2. Patients with oligomenorrhoea n=30	3. Patients with regular cycles n=27
Duration of infertility (years) X ± SD	4.42 ± 3.35	3.33 ± 1.32	4.8 ± 2.39

t-test for 1 and 2 p=0.440426; t-test for 1 and 3 p=0.768643; t-test for 2 and 3 p=0.067

Hyperolactinaemia is relatively often associated with other possible causes of infertility — in 35/78 (44.88%) patients (Table 5).

Table 5. Association of hyperprolactinaemia and other causes of infertility in our patients

Male factor	6/78	(7.69%)
Mechanical factor	4/78	(5.12%)
Endometriosis	5/78	(6.41)
Premature ovarian failure	3/78	(3.85%)
Chlamydia	3/78	(3.85%)
Asherman's syndrome	1/78	(1.31%)
Endometrial polyp	4/78	(5.12%)
Myoma	7/78	(8.97%)
Insulin resistance	2/78	(2.56%)

Hyperpolactinaemia as the only reason for anovulation and infertility was diagnosed in 43/78 (55.12%) of our patients. This group was separately analyzed. Amenorrhoea was present in 20/43 (46.51%), oligomenorrhoea in 12 (23.53%), and regular cycles in 11/43 (29.96%). Anovulatory cycles were present in all patients with amenorrhoea and oligomenorrhoea and their serum prolactin levels were the highest (Table 6).

Table 6. Serum prolactin levels in patients with hyperrolactinaemia as the only reason for infertility

	Patients with amenorrhoea[1] n=20	Patients with oligomenorrhoea[2] n=12	Patients with regular cycles [3] n=11
Serum prolactin levels (mIU/l) X ± SD	3255.0 ± 1646.78	1665.5 ± 1140.32	1519.0 ± 427.53

t-test for 1 and 2 p=0.03475; t-test for 1 and 3 p=0.033315; t-test for 2 and 3 p=0.71

There were 11 patients with regular cycles and elevated serum levels of prolactin as the only diagnosed cause for infertility. Inadequate luteal phase was diagnosed in 6/11 (54.54%) of those patients according to transvaginal ultrasound measurements of follicle diameter during menstrual cycle and the mid-cycle serum progesterone levels. Serum prolactin levels in patients with inadequate luteal phase were higher in comparison to serum PRL levels in patients with adequate luteal phase (1624.33±369.0 mIU/l vs 1189.33 ±166.63 mIU/l; p=0.03853).

There were 35 pregnancies in the whole group of infertile patients with hyperprolactinaemia (44.87%). This proportion of achieved pregnancies is higher in the group of patients with hyperprolactinaemia as the only cause of infertility —33/43 or 76.74% (Table 7). Two patients among them became pregnant again after the first delivery with spontaneously normalized serum prolactin levels. Table 7 shows the therapy for infertility in patients who achieved pregnancy.

Table 7. Treatment of infertility in patients with hyperolactinaemia who achieved pregnancy

Pregnancy after spontaneous cycles	7/33	(21.21%)
Bromocriptine only therapy	16/33	(48.49%)
Bromocriptine + clomiphene	6/33	(18.18%)
Bromocriptine + clomiphene + HCG + IUI	1/33	(3.03%)
Quinagolide	2/33	(6.06%)
Bromocriptine + IVF	1/33	(3.03%)

HCG, human chorionic gonadotrophine; IUI, intrauterine insemination; IVF, in vitro fertilization

There were only 2/35 (5.71%) patients who achieved pregnancy in the group of infertile patients with hyperpolactinaemia associated with other causes of infertility, which is statistically significantly different compared to the group of infertile patients with hyperprolactinaemia as the only cause of infertility (t=6.27319; p<0.05).

Cycles in hyperprolactinaemic infertile patients treated with bromocriptine became regular after 12.75 ± 8.68 weeks of the therapy.

Galactorrhoea ceased after 6.05 ± 0.07 weeks, but did not totally disappear in all cases.

Hyperprolactinaemic patients successfully treated for infertility achieved pregnancy after 8.75 ± 3.89 months of the therapy for hyperprolactinaemia (range from 1.5 to 24 months).

Bromocriptine, alone or in combination with clomiphene, was administered in 69/78 (88.46%) hyperprolactinaemic infertile patients. In the group of infertile patients treated with bromocriptine once a day, pregnancy was achieved in 7/34 (20.58%), and if bromocriptine was administered 2 or 3 times a day, 17/35 (48.57%) patients became pregnant (t=2.439964; p<0.05). Between these two groups of hyperprolactinaemic patients there were no differences in age: (29.0±8.44) years in the group with bromocriptine once a day vs. 29.75±7.38 years in the group with 2 or 3 daily doses of bromocriptine (t-test - p=0.899264); nor in duration of infertility (5.75±2.87 years vs. 4.25 ±2.5 years; t-test – p=0.408262).

Bromocriptine therapy was stopped in two patients due to visual disturbances. The first patient had visual hallucinations ("fire from the electric cooker") and the second patient experienced scintillations. Another three patients switched to quinagolide due to intolerance to bromocriptine. In most cases, initial intolerance was easily overcome with taking the first dose of bromocriptine immediately before sleeping or with gradually increasing the bromocriptine dose.

Outcome of the pregnancies was as follows: 19/35 were delivered *per vias naturalis*, with only one preterm delivery. Caesarean section was performed in 8/35 (22.86%) pregnancies. All children were vital and born at term, with one exception, born in 34th week, vital. After the treatment for hyperprolactinaemia, there were 5/35 (14.28%) spontaneous abortions, and 3/35 (8.57%) missed abortions.

Discussion

In most cases of hyperprolactinaemic infertile patients, treatments with control serum prolactin levels can easily restore ovulation and the great majority of such patients become pregnant. The problem exists in the proportion of hyperprolactinaemic patients with combination of hyperprolactinaemia and some other causes of infertility.

Combination of hyperprolactinaemia and endometriosis in infertile patient is especially difficult for treatment. There are many reports about hyperprolactinaemia in patients with endometriosis [9–11], as well as reports about positive correlation of serum prolactin levels and the stage of endometriosis [12–15]. There is also evidence that patients with endometriosis have at least occult hyperprolactinaemia, according to TRH (thyrotropin-releasing hormone) stimulation, with higher serum prolactin levels in patients who had not achieved pregnancy during the treatment for endometriosis [12, 16]. On the other hand, the impact of minimal and mild endometriosis to infertility is still unclear [7], even though the minimal and mild endometriosis have been found during laparoscopy in many infertile patients. The infertility in those patients was considered as idiopathic until laparoscopy was performed. Unfortunately laparoscopy is not a part of routine investigation of infertility in some countries [17]. Human decidua produces prolactin, and prolactin is considered to be a better endometrial marker than prostanoid or CA 125, because decidua and endometriotic implants are the only sources for prolactin in abdomen, which is not the case with CA 125, moreover receptors for prolactin are found in endometriotic tissue [18]. There is a hypothesis that the content of prolactin in peritoneal fluid depends only on the activity of endometriotic implants, but there are also opposite opinions that the prolactin secretion from those implants is negligible, without impact on infertility in these patients [19]. It was speculated that prolactin from endometriotic implants could be a reason for local ovarian dysfunction and inadequate luteal phase which is followed by spontaneous abortions. Some studies supported this hypothesis [20], and the other authors conclude that the endometriosis is associated with inadequate luteal phase, but aberrant prolactin secretion by endometriosis implants has nothing to do with that [21].

Prolactin has immunomodulatory role as up-regulator of immune processes, and hyperorlactinaemia is often present in autoimmune diseases [22]. It is possible that immunomodulator characteristics of prolactin are connected with association of hyperprolactinaemia and endometriosis.

Nocturnal prolactin peak is exaggerated and prolonged in patients with endometriosis [23]. Authors of the study concluded that disturbances of nocturnal prolactin secretion could contribute to occurrence of infertility in patients with endometriosis, and this is the part of pathophysiology of that disease. The question is which one is the primary: hyperprolactinaemic environment which makes individual susceptible to development of endometriosis or endometriotic implants that can secrete enough amounts of prolactin to cause hyperprolactinaemia and subsequent infertility [18].

Clinical experience showed that the treatment of patients with associated hyperprolactinaemia and endometriosis is complicated, and if the success is absent, the couple should be referred to IVF as soon as possible.

The other causes of infertility that could be associated with hyperprolactinaemia are premature ovarian failure (in 5.12% of our patients) and insulin resistance in hyperorlactinaemic anovulation (in 2.56% of our patients). Even though the proportion is small, those patients still deserve attention. Hyperprolactinaemia and polycystic ovarian syndrome are different conditions, but insulin resistance could be associated with both of them. The association of prolactinoma and polycystic ovarian syndrome is possible, which has already been reported [24]. This is important during the infertility treatment of those patients: if the treatment with bromocriptine improves insulin resistance, the connection of hyperprlactinaemia and insulin resistance is obvious. This was the case with both of our hyperprolactinaemic patients with insulin resistance, but the small sample precludes us from definitive conclusions.

The relation of hyperprolactinaemia and psychological stress due to infertility is a specific question. It is well known that elevated prolactin levels are physiological correlates of psychosocial stress response. The levels of prolactin are higher in emotional than in manipulative tears [25]. There are no clinical reports about the impact of psychosocial stress caused by infertility to serum prolactin levels in hyperprolactinaemic patients, but clinical experience showed that empathy, compassion and improvement of overall quality of life could improve the success of infertility treatment.

The possible causes of unexplained infertility are abnormal function of sperm and oocyte, disorders of fertilization, implantation and embryo development during early stages. Hyperprolactinaemia could exist parallel to such functional disorders, which should be kept in mind in cases when the pregnancy was not achieved despite of the successful treatment of hyperprolactinaemia, so patient should be referred to ART procedures. Yet, there is no evidence that hyperprolactinaemia is associated with the mentioned abnormalities, possible causes of idiopathic infertility.

The majority of our hyperprolactinaemic patients are treated with bromocriptine. In the beginning of the therapy, about one half of the patients had nausea and vertigo, but these side effects disappeared when the medication was taken immediately before going to sleep or with gradually increased the doses of bromocriptine. Total daily dose of bromocriptine could be divided in two or three smaller doses, which offers better control of circadian variations of prolactin serum levels, as well as better control of nocturnal prolactin levels. The majority of our infertile patients with hyperprolactinaemic anovulation achieved pregnancy with divided daily bromocriptine dose. Visual hallucinations that happened

with two of our patients during bromocriptine treatment could be explained by the fact that the molecule of bromocriptine is similar to molecule of LSD [7]. The patients should be warned that their concentration could decrease during the bromocriptine treatment, which is important for some jobs or during car driving. For patients that could not stand side effects of bromocriptine or in whom bromocriptine treatment failed the best choice is quinagolide [26].

Quinagolide is equally successful in the treatment of hyperprolactinaemia as bromocriptine [27], but there are also reports that quinagolide is superior to bromocriptine in the treatment of hyperpolactinaemia associated infertility [28, 29]. It is better to avoid cabergoline in early pregnancy, even though there are reports about its safety, we state that patients who desire pregnancy, should switch to bromocriptine or quinagolide. Among all dopamine agonists, cabergoline has the longest half life (65 hours), so it is possible to be administered once or twice a week, but also there is a chance for early pregnancy to be exposed to the effects of cabergoline. The biggest study reported till now has included over 300 cases and the incidence of foetal anomalies was not elevated [30]. Anyway, further clinical trials are still needed for definitive conclusions [31]. Taking into account the effects of cabergoline on immunological system and macrophages, possible development of cardiac valvulopathy and related disorders (pericarditis and pericardial effusion) [29, 32], it seems reasonable to avoid this drug in early pregnancy, especially that safety of bromocriptine and quinagolide in pregnancy is already proven.

Bromocriptine or quinagolide should be administered in hyperprolactinaemic patients who desire the pregnancy as long as needed for patient to achieve the pregnancy. In our patients with adequate prolactin suppression pregnancy was achieved after 8.75±3.89 months of therapy (range from 1.5 to 24 months). Bromocriptine is used from 1971 and till now there were no reported harmful effects on early pregnancy and it is considered safe.

About one fifth of our patients achieved pregnancy without the therapy for hyperprolactinaemia which could be explained by macroprolactinaemia: hyperolactinaemia due to excess macroprolactin with normal concetrations of bioactive monomeric prolactin [33]. Macroprolactin is composed of macromolecules — isoformes of prolactin (dimeric or trimeric molecules; big- and big-big prolactin) with little if any biological activity, but readily measured by standard assays. It was stated that the screening for macroprolactin should be a part of investigation in all hyperprolactinaemic patients because it could be a significant cause of misdiagnosis and inappropriate treatment [33, 34,].

Spontaneous abortions were noted as outcome in 8/35 (22.85%) patients who became pregnant after the therapy with bromocriptine, but this proportion was similar to the proportion of spontaneous abortions in general population. One half of our hyperprolactinaemic patients with secondary infertility experienced missed abortion before the treatment for hyperprolactinaemia, which allows us to make a hypothesis that elevated prolactin levels could be a reason, probably not only due to inadequate luteal phase or aberrant endometrial receptivity, but also due to some still unknown way.

If the pregnancy passes successfully through the first trimester, the outcome is usually the delivery of term and viable infant. The other studies have also reported that after successfully treating hyperprolactinaemia the incidences of spontaneous abortions, ectopic gravidities, preterm deliveries and other complications of pregnancy were not elevated [35].

During the lactation in patients with prolactinomas, there were no further growths of tumours [7, 35].

Spontaneously restored ovulatory cycles have already been reported after the delivery of successfully treated hyperprolactinaemic patients [7, 35–38]. Similar situation has also been noted in our patients: two of them became pregnant again without the therapy, year and a half and two years after the first delivery. In both of them serum prolactin levels were spontaneously normalized, which could be explained by pituitary infarcts developed during the shrinkage of microprolactinoma in pregnancy or spontaneous recovery of hypothalamic dysfunction responsible for lactotroph hyperplasia [7].

Conclusion

In one half of the infertile patients with hyperprolactinaemia, this is the only cause of infertility and in other half hyperprolactinaemia is associated with some other causes of female infertility.

The treatment of hyperprolactinaemia is obligatory in all patients with infertility. In our series, bromocriptine was successfully used in the majority of patients with infertility, with better effects when used in divided doses during all day.

If adequate suppression of serum prolactin levels is achieved, but the pregnancy is still missing despite the fact that ovulatory cycles are established, other causes of infertility should be searched for, and the clinician should not reject the possibility of existence of some unknown infertility factor, so the patient should be referred to assisted reproductive technology procedures which provide more chances in such circumstances.

The treated hyperprolactinaemia has no influence on pregnancy outcome.

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