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IDIOPATHIC HYPERPROLACTINAEMIA: A CLINICAL STUDY OF 140 PATIENTS

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Objective: Report the findings and experience in the management of 140 patient with idiopathic hyperprolactinemia treated at the King Fahd Hospital of the University, Al-Khobar, Saudi Arabia, and the effect of the treatment with Bromocriptine on the restoration of normal menstrual pattern and fertility.

Method: The study was conducted over a period of five years in 140 patients with idiopathic hyperprolactinemia who were investigated and treated at the Endocrinological, Infertility and Gynaecological Clinics at the King Fahd Hospital of the University, Al-Khobar between January 1988 to December 1992. The initial serum prolactin levels ranged from 28.5 to 224 ng/ml, with a mean of 62 ng/ml. Among the 140 patients with idiopathic hyperprolactinemia, 102 patients were complaining of infertility. All the patients in the study were treated with Bromocriptine to normalize serum prolactin or to achieve pregnancy.

Result: Out of the 102 infertile patients, 82 (80.3 %) achieved pregnancy with Bromocriptine therapy alone, and the remaining 20 patients received additional treatment with Clomiphene and Human Chorionic Gonadotrophin for induction of ovulation. A total of 88 (86.2 %) patients achieved pregnancy, 76 had full term pregnancy and 12 ended with abortion. There was no significant difference in the pregnancy rate, between the patients with initial low serum prolactin levels and those with high levels. Similarly, the presence of galactorrhea did not influence the pregnancy rate. No lethal congenital foetal abnormalities were observed in the patients.

Conclusion: Bromocriptine therapy in the treatment of hyperprolactinemia is safe and effective resulting in high pregnancy rate and resumption of normal menstrual pattern.

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Idiopathic hyperprolactinemia with no demonstrable pituitary or central nervous system disease and without any recognized cause of increased prolactin secretion is the most common disorder of the hypothalamic-pituitary axis and has been found in up to 25 % of patients with secondary amenorrhea[1-3].

The estimation of serum prolactin level is routinely done in the investigation of patients with amenorrhea, galactorrhea and infertility and has led to an increased recognition of hyperprolactinemia. Until the discovery of Bromocriptine, all cases of hyperprolactinemia were thought to be a consequence of prolactinoma and treated with surgery. But with the development of Bromocriptine which is a specific dopamine receptor agent, all various hyperprolactinemic conditions were treated medically[4-6].

The purpose of this paper is to report our findings and experience in the management of 140 patients with idiopathic hyperprolactinemia treated at the

King Fahd Hospital of the University, Al-Khobar, Saudi Arabia, and to prove the efficacy of Bromocriptine in restoring normal menstrual pattern and fertility with high pregnancy rate in a substantial number of patients.

METHODS

The study was conducted over a period of five years from January 1988 to December 1992. All patients were diagnosed to have idiopathic hyperprolactinemia. It was our practice to start all patients who were hyperprolactinemic on increasing doses of Bromocriptine (Parlodel by Sandoz-Switzerland) till a normal serum prolactin level of 20 ng/ml was achieved. We stopped the drug immediately after pregnancy was diagnosed in those patients who were trying to get pregnant.

Included in the study were 140 patients between 18 and 42 years of age (mean age, 24 years) with a raised serum prolactin level who were investigated and treated at the Endocrinological, Infertility and Gynaecological Clinics at the King Fahd Hospital of the University, Al-Khobar, Saudi Arabia. The majority of the patients were below the age of 30 years, 94 (67 %). A provisional diagnosis of hyperprolactinemia was made if a single laboratory value was more than 20 ng/ml. The diagnosis of idiopathic hyperprolactinemia was made after excluding pituitary tumour by skull x-ray and/or CAT scan and other causes of hyperprolactinemia such as thyroid disease, antidepressants, antihypertensive drugs and oral contraceptive pill.

All patients included in the study presented initially either with complaints of infertility, amenorrhea, menstrual irregularities and/or galactorrhea. Some of the patients presented with more than one complaint at a time. The majority of our patients were complaining of infertility, 102 (72.8 %). A complete history was recorded on a standardised form noting the patient age, parity, previous obstetric history, duration of menstrual irregularities, amenorrhea, infertility, galactorrhea, past medical and surgical history, medication received and the results of clinical laboratory investigations. For statistical analysis the t-test was used and P value < 0.05 was considered significant.

The following laboratory analyses were also performed; thyroid function tests, follicular and luteinizing hormone, dehydroepiandrosterone sulphate, testosterone and pelvic ultrasound to exclude polycystic ovarian disease, primary hypothyroidism and primary ovarian failure. In infertile couples, semen analysis of the husband and tubal pregnancy of the patient were tested by hysterosalpingography or laparoscopy and dye studies.

A skull x-ray together with CAT scanning of the pituitary was performed to exclude pituitary lesions in all the patients in whom the prolactin level was above 50 ng/ml. The remaining patients had lateral x-ray of the skull only.

In those patients with regular menstrual cycles, in addition to hormonal profile tests, a pelvic ultrasound was also done to see if ovulation was present.

Bromocriptine was administered orally in doses varying from 2.5 to 15 mg daily. The dose scheduled for each patient was individualized depending upon the clinical and laboratory response. Patients were maintained on the lowest dose compatible with normal measurements of serum prolactin levels which are in our laboratory 20 ng/ml. Bromocriptine was stopped as soon as a patient was diagnosed to be pregnant. If ovulation was not evident in infertile patients with normalization of serum prolactin levels, additional treatment with Clomiphene (Clomid by Marion Merrell Dow-Italy) and Human Chorionic Gonadotrophin (Pregnyl by Organon - Holland) were added to the treatment regimen to induce ovulation. All patients included in the study were followed up for a period of two years after the treatment.

RESULTS

The serum prolactin level ranged from 28.5 to 224 ng/ml. The frequency distribution of prolactin levels are shown in Table 1. Of the 140 patients 71 (50.7 %) had prolactin levels less than 50 ng/ml. Only three patients had prolactin levels more than 200 ng/ml. The remaining 66 patients had prolactin levels ranging between 51-200 ng/ml.

Table 1. Prolactin level (ng/ml) in 140 patients

Serum prolactin (ng/ml)	Number	Percentage (%)
21-50	71	50.7
51-100	46	32.8
101-200	20	14.4
> 200	3	2.1
Total	140	100.0

Of the 140 patients with idiopathic hyperprolactinemia 132 (94.2 %) achieved normal prolactin levels which is in our laboratory 20 ng/ml within 4-6 weeks of starting Bromocriptine treatment with 2.5-5 mg daily. The remaining 8 patients achieved normal prolactin levels with higher doses of Bromocriptine 10-15 mg daily.

Among the 102 infertile patients 82 (80.3 %) achieved pregnancy with Bromocriptine therapy alone, and the remaining 20 patients received additional treatment with Clomiphene and the Human Chorionic Gonadotrophin for induction of ovulation. Pregnancy occurred at an average of 8-12 weeks in patients treated with Bromocriptine alone and 12-18 weeks in patients who required additional treatment with Clomiphene and Human Chorionic Gonadotrophin. The pregnancy rate and outcome of pregnancy are shown in Table 2. Among the 20 patients who received additional treatment with Clomiphene and Human Chorionic Gonadotrophin for induction of ovulation 6 patients achieved pregnancy. In the remaining 14 patients menstruation became regular and ovulation was evident in all of them. The presence of galactorrhea and the level of the initial serum prolactin did not affect the pregnancy rate. There was no significant difference in the pregnancy rate between the patient with initial low serum prolactin levels and those with high level (P value was not significant). Twelve (13.6 %) pregnancies, ended in first trimester abortions.

Table 2. Pregnancy rate and outcome of pregnancy in 102 infertile patients

Serum prolactin	Total No.	Live Birth	Abortion	Percentage (%)
21-50	56	43	6	87.5*
51-100	31	22	4	83.8*
101-200	13	9	2	84.6*
> 200	2	2	0	100.0
Total	102	76	12	86.2

* P value was not significant

The menstrual period of the 105 patients who were complaining of irregular period and amenorrhea became regular within 2 to 4 months of medication.

Likewise Galactorrhea also ceased within 3 to 4 months in all 56 patients who had this condition. Among the infertile patients and those with irregular period 15 patients were diagnosed to have a polycystic ovarian disease with LH to FSH ratio of 3.1:1. The diagnosis was confirmed by ultrasound.

DISCUSSION

Long-term prospective studies of women with idiopathic hyperprolactinemia are important to see whether those patients will develop pituitary tumours later in their life.

Before the diagnosis of idiopathic hyperprolactinemia can be made, the presence of pituitary tumour must be excluded. Knowledge of whether or not a patient with hyperprolactinemia has a pituitary tumour is necessary because these tumours may become symptomatic during pregnancy[7-10].

Our approach to diagnosis idiopathic hyperprolactinemia is to evaluate the pituitary space by computed tomography scan in all patients in whom the prolactin level was above 50 ng/ml. The remaining patients had lateral x-ray of the skull. With this approach, some authors believe that, serum prolactin levels are not informative and plain x-ray of the sella turcica is inadequate to diagnose pituitary prolactinoma. Although small number of pituitary microadenoma may be misdiagnosed by this approach, their primary treatment is the same as for idiopathic hyperprolactinaemia[11-14].

Prolactin secretion is controlled by hypothalamic neurons that produce dopamine to inhibit its release. Disturbance of this inhibitory control results in hyperprolactinemia. Mild increase in the circulating prolactin (20-50 ng/ml) may inhibit ovulation or cause an inadequate corpus luteum resulting in infertility even in patient with regular menstrual cycle as in some of our cases. Severe hyperprolactinemia (> 100 ng/ml) usually produces amenorrhea, galactorrhea and a hypo-estrogenic state.

The treatment of hyperprolactinemia and galactorrhea is individualized according to the patient's requirements. Obviously the treatment of anovulation in an infertile or amenorrhic patient will be directed towards induction of ovulation and elimination of troublesome lactation in galactorrhic patients. The introduction of Bromocriptine in clinical practice has revolutionised the treatment of patients with functional or organic hyperprolactinemia. Bromocriptine, in adequate doses, lowers the plasma prolactin level and restores menstruation and ovulation in 80 % of patients. In the present series 80.3 % of the patients desiring pregnancy achieved it within 8 to 12 weeks of starting the Bromocriptine therapy and normal menstrual pattern was established in the majority of patients[15-21].

All except 12 patients carried the pregnancy to full-term and deliver healthy babies. The incidence of abortion at 13.6 % in the study group was slightly higher than the overall abortion rate of 10.6 % for the hospital. Bromocriptine was stopped as soon as a patient was diagnosed to be pregnant. Therefore, it is highly unlikely for it to have a role in the aetiology of abortion. No congenital malformations were detected in the babies born in this series. The incidence of congenital malformations following Bromocriptine therapy reported in the literature is not higher than the normal population[22-24].

CONCLUSION

Ovulation can safely be induced with Bromocriptine in infertile patients with idiopathic hyperprolactinemia with a high pregnancy rate and resumption of normal menstrual pattern. However long-term Bromocriptine therapy is unnecessary, since it may lead to prolactinoma.

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