IDIOPATHIC HYPERPROLACTINAEMIA: A CLINICAL STUDY OF 140 PATIENTS

Ali I Al-Sultan, MD, FRCP-C*Sulaiman S Al-Najashi, M.Med(O/G)**

Objective: Report the 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 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.
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

<table>
<thead>
<tr>
<th>Serum prolactin (ng/ml)</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-50</td>
<td>71</td>
<td>50.7</td>
</tr>
<tr>
<td>51-100</td>
<td>46</td>
<td>32.8</td>
</tr>
<tr>
<td>101-200</td>
<td>20</td>
<td>14.4</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>140</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Serum prolactin (ng/ml)</th>
<th>Total No.</th>
<th>Live Birth</th>
<th>Abortion</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-50</td>
<td>56</td>
<td>43</td>
<td>6</td>
<td>87.5*</td>
</tr>
<tr>
<td>51-100</td>
<td>31</td>
<td>22</td>
<td>4</td>
<td>83.8*</td>
</tr>
<tr>
<td>101-200</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>84.6*</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>76</td>
<td>12</td>
<td>86.2</td>
</tr>
</tbody>
</table>

* 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.

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.

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 amenorrheic patient will be directed towards induction of ovulation and elimination of troublesome lactation in galactorrhetic 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.

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 etiology 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.

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.
REFERENCES


