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Management of Infertile Hyperprolactinemic Women in Infertility Clinic in Mosul City

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ABSTRACT

Background: The diagnosis of hyperprolactinemia depends on the measurement of circulating prolactin in an appropriate clinical setting. Thus women with oligomenorrhea, amenorrhea, galactorrhea, or infertility must have their serum prolactin levels be measured.

The aim: The present study aimed to detect and manage infertile women with hyperprolactinemia and assess the effectiveness of therapy to achieve conception.

Study Design and Methods: This case series study included all women who were registered in the Infertility and IVF Center in Al-Batool Maternity Teaching Hospital in Mosul city during the period from 1st Jan. 2004-31st Dec. 2005. The patients were assessed by the gynecologists through thorough history, physical examination and hormonal analyses. The diagnosis of hyperprolactinemia among these cases was documented. Patients were treated and followed for one year with bromocriptine alone for first three months, followed by combination of clomiphene citrate and human chorionic gonadotrophin with bromocriptine for the next 6 months and lastly gonadotrophines was used instead of clomiphene citrate for the last 3 months.

Results: Hyperprolactinemia accounts of 15.7% of the study sample. A highly significant association (P=0.001) between patients' prolactin values and menstrual disorders. The overall pregnancy rate was 70.1% where 40.8% of cases had pregnancy during the first three months.

Conclusion: Early and prompt diagnosis of hyperprolactinemia among registered women with reproductive problems along with adequate and individualized dose of therapy; primarily with dopamine agonists, are successful in solving infertility problem in most of the cases.

Keywords: Bromocriptine, galactorrhea, Hyperprolactinemia, Infertility, Mosul.

INTRODUCTION

Hyperprolactinemia is one of the most common causes of reproductive problems encountered in clinical practice [(1)]. Prolactin is related to certain functions such as mammary gland growth, lactation, stress response and immune system development [(1,2)]. Thus women presented with oligomenorrhea, amenorrhea, loss of libido, galactorrhea, and infertility must have their serum prolactin levels be measured [{1,2}].

The usual normal range for serum prolactin in non-pregnant women is 5-20 ng/ml. An excess of prolactin above a reference laboratory's upper limit or "biochemical hyperprolactinemia" (serum prolactin >20 ng/ml) is one of the most frequent endocrine causes of infertility.

The diagnosis of hyperprolactinemia depends on the measurement of circulating prolactin in an appropriate clinical setting [(3,4)]. Its prevalence depends on the study population where among healthy adults is up to 3% [(5)]; however the rate is higher among patients with specific symptoms related to hyperprolactinemia; i.e. among women with amenorrhea the rate is found to be 9% and among those with galactorrhea is up to 25%. Moreover, the rate of hyperprolactinemia is as high as 70%

among those with both amenorrhea and galactorrhea [6,7]. The etiology hyperprolactinemia may be physiological, pharmacological or pathological; however, in cases where all causes of have been excluded and no adenoma can be visualized with magnetic resonance imaging (MRI), it is referred to as "idiopathic"[8,9].

Medical therapy has traditionally involved dopamine agonists which is the physiologic inhibitor of prolactin. Although initially it was thought that patients would require dopamine agonist therapy all their lives; however the current use of these agents is based on the patient's needs and circumstances [3,8]. Dopaminergic treatment is highly effective for both idiopathic and tumoral hyperprolactinemia [8].

The present study aimed to estimate the frequency of hyperprolactinemia among infertile women registered in the Infertility and IVF Center in Al-Batool Maternity Teaching Hospital in Mosul city and to assess the effectiveness of their management.

PATIENTS AND METHODS

All women registered in the Infertility and IVF Center in Al-Batool Maternity Teaching Hospital in Mosul city during the period from 1st Jan. 2004 to 31st Dec. 2005 were enrolled in this study. After giving their formal consent, these patients were assessed by the gynecologists through thorough history and physical examination including general and pelvic examinations as well as laboratory tests.

The patients' male partners were assessed and managed by the urologist and each registered couple was provided by special return card. Samples of peripheral blood were taken from infertile women for hormonal analyses on day three of the menstrual cycle such as Follicle Stimulating Hormone (FSH); Luteinizing Hormone (LH); estradiol (E2) and Prolactin (PRL); while progesterone was performed on day 21 of the menstrual cycle. In women with evidence of hyperandrogenism, serum Testosterone was done.

The diagnosis of hyperprolactinemia in these cases was documented when serum prolactin levels were found on two separate occasions to be above 20 ng/ml [10]. In addition, cases were classified according to their prolactin level into: mild degree of hyperprolactinemia, when serum prolactin values of 20-50 ng/ml. While moderate degree of hyperprolactinemia, includes serum prolactin of 50-100 ng/ml and severe degree when serum prolactin values is greater than 100 ng/ml [10]. In certain cases thyroid function test, MRI of the head and visual field test were carried out to exclude pathological causes of hyperprolactinemia.

Monitoring of ovulation in all cases was performed by serial vaginal ultrasonography and serum estradiol. Those couples with normal male partners, the treatment of hyperprolactinemia in female partners was established with careful monitoring of PRL and ovulation throughout the individually management period that ranged between 3-12 months. The treatment was initiated by bromocriptine alone for the first three months, which was started with 1/2 tablet of bromocriptine daily and then increased gradually every 3-4 days till it ranged between 2.5-7.5 mg daily.

It was used as individual dosage according to the severity of the hyperprolactinemia and treatment with bromocriptine is stopped as soon as pregnancy is diagnosed; however if no response was detected, clomiphene citrate (CC) and human chorionic gonadotrophin (HCG) were added for a period of six months with individual dose of CC ranged between 50-150 mg daily. When this regimen failed, gonadotrophines (Humegon) was used with the above regimen for the last three months instead of CC [11].

RESULTS

Data of the results showed that the total number of women registered in Infertility and IVF Center in Al-Batool Maternity Teaching Hospital in Mosul city was 1582 during the study period from 1st Jan 2004-31st Dec 2005. However; 1290 (81.5%) of the registered women were investigated thoroughly and managed accordingly while the remainders were drop-out of the study sample because they did not complete their investigations and follow-up.

(Table 1) reveals that more than half (51.9%) of the infertility cases in the study sample were due to female factors, while male partners were responsible for almost one third of cases (30.4%). Data of the results also showed that 203 (15.7%) of the study sample were found to have hyperprolactinemia.

Table 1: Distribution of study sample according to the etiology of infertility.

Etiology of Infertility	Registered Patients	
	No.	%
Male Factors	392	30.4
Female Factors	670	51.9
Male & Female (Combined) Factors	153	11.9
Unexplained Factors	75	5.8
Total	1290	100.0

The data demonstrated that almost three fifths (59.1 %) of the cases had mild prolactinemia and more than one-third (34.0%) had moderate prolactin level while minority (6.9%) had severe prolactinemia of which two cases were referred to neurosurgeon and they were found to have pituitary tumour and managed there accordingly (Table 2). Thus, the total number of patients who managed as functional hyperprolactinemia was 201.

Table 2: Distribution of patients with hyperprolactinemia according to the degree of hyperprolactinemia.

Degree of Hyperprolactinemia (Prolactin level)	Hyperprolactinemic Patients	
	No.	%
Mild Hyperprolactinemia (20-50) ng/ml	120	59.1
Mod Moderate Hyperprolactinemia (50-100) ng/ml	69	34.0
Severe Hyperprolactinemia (>100) ng/ml	14	6.9
Total	203	100.0

A highly significant association (P=0.001) was detected between patients' PRL values and their menstrual cycle, where 78.6% of patients with higher PRL values (>100 ng/ml) had amenorrhea while on the other hand almost two-thirds (62.5%) of those with mild hyperprolactinemia had regular menstrual cycle (Table 3). However data of the results showed no significant association between the degrees of hyperprolactinemia and presence of galactorrhea as expressed by (Table 4).

Table 3: The relationship between the degree of hyperprolactinemia and the regularity of menstrual cycle among patients with hyperprolactinemia

Degree of Hyperprolactinemia (Prolactin level)	Hyperprolactinemic Patients						Total
	Regular Cycle		Irregular Cycle		Amenorrhea		
	No.	%	No.	%	No.	%	
Mild Hyperprolactinemia (20-50) ng/ml	75	62.5	38	31.7	7	5.8	120
Moderate Hyperprolactinemia (50-100) ng/ml	19	27.5	39	56.5	11	15.9	69
Severe Hyperprolactinemia (>100) ng/ml	1	7.1	2	14.3	11	78.6	14
Total	95	46.8	79	38.9	29	14.3	203

$X^2 = 72.429$, d.f = 4, P = 0.001.

Table 4: Association between the degree of hyperprolactinemia and the presence of galactorrhea among patients with hyperprolactinemia.

Degree of Hyperprolactinemia (Prolactin level)	Galactorrhea				Total No.
	Positive		Negative		
	No.	%	No.	%	
Mild Hyperprolactinemia (20-50) ng/ml	42	35.0	78	65.0	120
Moderate Hyperprolactinemia (50-100) ng/ml	26	37.7	43	62.3	69
Severe Hyperprolactinemia (>100) ng/ml	4	28.6	10	71.4	14
Total	72	35.5	131	64.5	203

$X^2 = 0.450$, d.f = 2, N.S.

(Table 5) indicates that the overall pregnancy rate was 70.1% where 40.8% of cases had pregnancy during the first three months with bromocriptine treatment only and 39.5% of those managed by using bromocriptine, CC and HCG.

Table 5: Effectiveness of patients' management.

Type of Therapy	T Treated Patients No.	Pregnant Patients	
		No.	%
Bromocriptine Only	201	82	40.8
Bromocriptine + Clomiphene Citrate + HCG	119	47	39.5
Bromocriptine + Gonadotrophines	72	12	16.7
Total Treated Patients	201	141	70.1

A highly significant association (P=0.001) was found between different degrees of hyperprolactinemia and duration of therapy among patients being pregnant, where more than two third (70.1%) of patients with mild degree of hyperprolactinemia being pregnant during the first three months of management while almost one third (31.8) of those patients with moderate and severe hyperprolactinemia did so during the same period (Table 6).

Table 6: Association of degree of hyperprolactinemia and duration of therapy among pregnant patients

Degree of Hyperprolactinemia (Prolactin level)	No.	T Total Pregnant Patients		Pregnant Patients during					
				≤ 3 months		3-9 months		9-12 months	
		No.	%	No.	%	No.	%	No.	%
Mild Hyperprolactinemia	120	97	80.8	68	70.1	23	23.7	6	6.2
Moderate and Severe Hyperprolactinemia	81	44	54.3	14	31.8	24	54.6	6	13.6
Total Treated Patients	201	141	70.1	82	58.2	47	33.3	12	8.5

$X^2 = 18.237$, d.f = 2, P = 0.001

DISCUSSION

A systematic and efficient evaluation of an infertile couple is of great importance in order to identify the cause of infertility, provide a basis of potentially successful treatment and offer emotional support [12].

Data of the results showed that females were responsible for 51.9% of the infertility cases; while almost one third (30.4%) of cases were due to male factors. Combined factors and unexplained infertility found in 11.9% and 5.8% of the study sample respectively. The same results had been confirmed by Ayoub in 1992 in her study in Mosul city [13], where she indicated that female factors were the main etiological factor in infertility and was reported in 56.2% of infertile couples, and male factor accounts for 20%; while both male and female had shared in their infertility in 15% of infertile couples and lastly 8.8% had no obvious cause for infertility. Similarly Rein and Schiff in Italy [12] reported that the major categories (55%) of infertility were due to female factors while male factor contributing to 35%.

Data of the results indicated that 15.7% of the study participants were found to have hyperprolactinemia. A higher figure (28.7%) was reported by Dragojevic et al [14] in their study in Belgrade. This difference may be due different study settings and methodology.

Data of the results indicated that 35.5% of hyperprolactinemic infertile women presented with galactorrhea and no significant association was detected between the degrees of hyperprolactinemia and presence of galactorrhea. This is similar to that reported by other authors [15-18], where they reported that the incidence of galactorrhea in hyperprolactinemic patients is 30-80%, depending on the skills of the examiners. However approximately 50% of women with galactorrhea have normal prolactin level and on the other hand those patients with very high prolactin levels i.e greater than 100 ng/ ml often have no galactorrhea. Thus it is regarded as a poor marker of hyperprolactinemia that in patients with extremely high prolactin levels; galactorrhea may not be found [8]. It was also documented that medical therapy can also be effective in restoring fertility in the patients with galactorrhea regardless of prolactin levels [19].

The results also showed that 53.2% of the study sample had menstrual abnormalities (irregular cycle and amenorrhea). Suleiman et al stated that oligoamenorrhea- and amenorrhea were the most frequent symptoms at presentation whereas galactorrhea occurred less frequently [4]. Data of the present study indicated a significant association (P=0.001) between the degrees of hyperprolactinemia and menstrual disorders, where only 5.8% of women with mild degree of hyperprolactinemia had amenorrhea; however a majority (78.6%) of those with severe degree of hyperprolactinemia presented with amenorrhea. This is in agreement with the findings of earlier study conducted by Ayoub in Mosul city [13].

This association may be explained by the fact that the symptoms of hyperprolactinemia in premenopausal women correlate with its severity, where PRL values >100 ng/ml is typically associated with overt hypogonadism, subnormal estradiol secretion and its consequences, including amenorrhea, hot flushes and vaginal dryness. Mild degree of hyperprolactinemia may only cause insufficient progesterone secretion and therefore, short luteal phase of menstrual cycle. Mild hyperprolactinemia can cause infertility even when there is no abnormality of the menstrual cycle, these women account for about 20% of those evaluated for infertility [10,12].

Data of the results also indicated that 14 (6.9%) of cases had severe prolactinemia of which two cases (PRL values were 940 and 720 ng/ ml respectively) were referred to neurosurgeon and they were found to have pituitary tumor and managed there accordingly. The most common tumor resulting in hyperprolactinemia is the pituitary prolactinoma (a benign growth of the prolactin-secreting cells of the anterior pituitary gland). Autopsy reports indicate that prolactinomas are present in 10-30 % of the population [20]. A level greater than 200 ng/ ml is almost always associated with prolactinoma or other prolactin-secreting tumor, and there is a relatively linear relation between the degree of prolactin elevation and the size of a true prolactinoma [3].

Dopamine agonists have become the treatment of choice for the majority of patients with hyperprolactinemic disorders [1, 9]. Bromocriptine was the first dopamine agonist to be used in medical practice and it is effective in normalizing serum PRL and restoring gonadal function in 80-90% of patients [21]. The present study revealed that pregnancy rate was achieved in 70.1% of hyperprolactinemic patients. Similar finding was documented by other authors where they reported that pregnancy rates of 60-80% can be achieved among these patients [11, 22]. Hardy and Fox stated that the response is usually rapid and if ovulation not seen within 2 months of normalizing PRL, CC can be added to the regimen. Human chorionic gonadotrophin is also used for patients who fail to ovulate on CC or who fail to conceive after 4-6 ovulatory cycles with CC [11].

CONCLUSION

This study concluded that early and prompt diagnosis of hyperprolactinemia at the beginning of infertility examination as well as adequate and individualized dose of therapy (primarily with dopamine agonists), are successful in solving infertility problem in most of the cases. In future studies, it is interesting to test how long the normal values of prolactin can be maintained after stopping therapy and whether there is a relation with its initial values, duration of therapy and dose of regimen.

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