ORIGINAL RESEARCH PAPER

Gynaecology

PATTERN OF CLINICAL PRESENTATION OF HYPERPLOLACTINEMIA AMONG INFERTILE PATIENTS

KEY WORDS:

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ABSTRACT

INTRODUCTION– The prevalence of hyperprolactinemia ranges from 0.4% in unselected normal adult females to as high as 9%–17% in females with reproductive health disorders.The etiology of hyperprolactinemia maybe pathological, physiological or pharmacological Drugs that stimulate the hypothalamic dopamine system and/or pituitary or dopamine receptors can cause elevated prolactin.Clinical features of hyperprolactinemia include menstrual disturbances (Oligo-amenorrhea, amenorrhea and irregular menses), anovulation, infertility galactorrhea or a combination of the above symptoms.

MATERIAL AND METHOD- This is a retrospective of 88 Infertile females with documented Hyperprolectinimea. The clinical data and infertility workup (Hormonal profile, Imaging report and other tests)were obtained from gynaecological OPD.

RESULTS- In this study the maximum number 54 (61.36%) of patientswere in the 21-25 years of age group, 65 (73.86%) of patients were of normal weight and 20 (22.72%) of patients were overweight only 3 (3.40%) were obese

In this study, the maximum number 60(68.18%)of patients were in primary infertility and 85 (96.59%) of patients had in mild rise in the prolactin level group.

In this study, most of the patients 27 (30.68%) of patients were presented with complaints of oligomenorrheaand followed by Amenorrhea 21 (23.86%). Galactorrhea was found in 25(28.40%) patients after clinical examinations,both amenorrhea and galactorrhea were seen in20(22.72%)of the patients. Hypothyroidism was present in 13 (14.77%) of patients.

CONCLUSION– Anovulatory cycle, Luteal face defect and sex hormonal imbalance caused by hyperprolactinemia results in infertility.Prolactin may stop ovulation and cause amenorrhea, in less severe cases Intermittent ovulation or ovulation that takes a long time to occur causes infrequent or irregular periods. that's why estimation of serum prolactin should be done at an early stage of an infertility workup. In our study, the prevalence of hyperprolactinemia and hypothyroidism was found very high which emphasize the importance of estimating TSH and Prolactin in infertility. In our study Oligomonorrhea, amenorrhea and galactorrhea are the commonest presentations in hyperprolactinemia. Proper Diagnosis and treatment results in an improvement in symptoms and an increase in conception rates in infertile patients.

INTRODUCTION

Hyperprolactinemia is a common endocrine disorder with gonadal dysfunction.

The prevalence of hyperprolactinemia ranges from 0.4% in unselected normal adult females to as high as 9%–17% in females with reproductive health disorders.[1,2]Its prevalence was found to be 5% in a family planning clinic, 9% in women with adult-onset amenorrhea, and 17% among women with polycystic ovary syndrome.[1]

Prolactin (PRL) is an anterior pituitary hormone that has its principle physiological action in the initiation and maintenance of lactation. In human reproduction, pathological hyperprolactinemia most commonly present as an ovulatory disorder and is often associated with secondary amenorrhea or oligomenorrhea.

Normal ovarian follicular development and oocyte release requires appropriate pituitary secretions of follicles stimulation hormones (FSH), luteinizing hormone (LH) as well as a lactogenic hormone, prolactin (PRL). The secretion of LH and PRL is regulated by Dopamine. Dopamine causes inhibition of pulsatile secretion of gonadotropin-releasing hormone (GnRH).

The etiology of hyperprolactinemia maybe pathological, physiological or pharmacological Drugs that stimulate the hypothalamic dopamine system and/or pituitary or dopamine receptors can cause elevated prolactin.[3,4]

Pathological causes of hyperprolactinemia in addition to a PRL secreting pituitary adenoma (Prolactinemia) and other pituitary tumors that produce acrology and Cushing diseases Including hypothalamic diseases, various pharmacologic agents, hypothyroidism chronic renal diseases or any chronic type of breast nerve stimulation, such as may occur with thoracic operation herpes zoster or chest trauma.[5]

Prolactinomas account for 25%–30% of functioning pituitary tumors and are the most frequent cause of chronic hyperprolactinemia.[6] Pathological hyperprolactinemia can also be caused by nonhypothalamic-pituitary disease.

In the absence of the above conditions if there is an elevation of serum prolactin (PRL) Idiopathic hyperprolactinemia may be there.

One of the most frequent causes of galactorrhea and hyperprolactinemia is the ingestion of pharmacologic agents, particularly tranquillizers, narcotics, and antihypertensive agents (Box 39.2). Of the tranquillizers, the Diaz epan and phenothiazines can produce hyperprolactinemia by decreasing the hypothalamic circulation of dopamine or by blocking its binding sites and therefore decreasing dopamine action.

primary hypothyroidism can also produce hyperprolactinemia and galactorrhea because of decreased negative feedback of thyroxine (T) in the hypothalamic-pituitary dis The resulting increase in TRH stimulates PRL secretion and thyroid-stimulating hormone (TSH) secretion from the pain itary. Approximately 3% to 5% of individuals with hyperprolactinemia have hypothyroidism. Therefore TSH, the most sensitive indicator of hypothyroidism, should be measured in all individuals with hyperprolactinemia. About 40% of patients with primary hypothyroidism have a mild elevation of prolactin levels that can be normalized by thyroid hormone replacement. Approximately 3-10% of women with PCOS have coexistent modest hyperprolactinemia.[7]

Clinical features of hyperprolactinemia that lead the patient

to seek medical advice include infertility, menstrual disturbances (oligo-amenorrhea, amenorrhea), anovulation, galactorrhea or a combination of the above symptoms. Approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Of these patients, approximately 30% have PRL- secretion tumors.

The presence of a pituitary tumor may cause headache or visual-field defects. increased body weight is associated with a PRL-secreting tumour. Osteopenia is observed in patients with associated hypogonadism and the degree of bone loss is related to the duration and severity of hypogonadism.

The diagnosis of hyperprolactinemia is made when serum prolactin levels are found on two different occasions to be above the upper limits of the established reference range (usually 20–25 ng/ml) or if the levels of prolactin are increased with the symptoms suggestive of hyperpro lactinemia.

If hyperprolactinemia is present without an identified cause imaging of the hypothalamic-pituitary area is required. A nonfunctioning pituitary adenoma or craniopharyngioma compressing the pituitary stalk may cause a mildly elevated serum prolactin level but high prolactin levels are mostly associated with a prolactin-secreting prolactinoma.[1] Although computerized axial tomography (CAT) scan can be used, magnetic resonance imaging (MRI) with gadolinium enhancement provides the best visualization of the sellar area. if the prolactin level is greater than 250 ng/mL a prolactinoma is most likely to be present[25] and a level of 500 ng/mL or greater is diagnostic of a macroprolactinoma. Selected drugs including risperidone and metoclopramide may cause prolactin elevations above 200 ng/mL.[8]

Dopamine Agonist is effective in normalizing prolactin, restoring hypothalamic-pituitary-gonadal axis function and reproductive hormones, Shrinking adenomas and subsiding galactorrheaCabergoline is a long-acting dopamine receptor agonist and is currently preferred over bromocriptine for primary therapy because of greater efficacy and fewer side effects [9], (1992 Wang, 2012). This agent directly inhibits pituitary lactotroph thereby decreasing PRL secretion. It is given orally in doses of 0.25 to 1 mg twice weekly. The initial dose is half a 0.5 mg tablet twice a week.[5] The initial operative cure rate for microadenomas is approximately 80% and 30% for macroadenomas, but the long-term recurrence rate is at least 20% for each.

MATERIAL AND METHOD

This study aimed toidentifythe pattern of clinical presentation of hyperprolactinemia among infertilepatients attendinggynecOPD.

This is a retrospective of 88 Infertile females with documented Hyperprolectinimea.

Detailed information was collected like age, BMI medical, menstrual, obstetric history, symptoms, general detailed clinical examination. All investigations – complete haemogram with, ESR Hormonal profile, (LH, FSH Serum prolactin TSH), Imaging report and other tests were obtained from gynaecological OPD and associated pathology clinic.Hyperprolectinimea at PRL levels of >25 Ng/ml.

All the data were analyzed using IBM SPSS Ver.20 software. Cross tabulation and frequency distribution were used to prepare tables. Data are expressed as numbers, percentage and mean.

RESULTS

88 infertile patients with hyperprolactinemia were included in the study.The Characteristics of the patients are following.

Table:- 1. Age distribution of Study group.

Age (in a year)	No	%
<20	5	5.68
21-25	54	61.36
26-30	18	20.45
30-35	8	9.09
36-40	2	2.27
>40	1	1.13
Total	**88**	**100**

In this study, the maximum number 54 (61.36%) of patients were in the 21-25 years of age group followed by 18(20.4%) in the 26-30 age group.

Table:-2 BMI Distribution of study group

BMI Distribution	No.	%
<19 (underweight)	0	0
19-24.9 (normal)	65	73.86
25-29.9 (overweight)	20	22.72
>30 (obese)	3	3.40
Total	88	100

In this study, the maximum number 65 (73.86%) of patients were of normal weight and number 20 (22.72%) of patients were overweight only 3 (3.40%) were obese.

Table:-3 Infertility types of the study group

Type Of Infertility	No.	%
Primary	60	68.18
Secondary	28	31.81
Total	88	100

In this study, the maximum number of 60(68.18%) patients were of primary infertility.

Table:- 4Hyperprolectinimea according to Serum prolactin levels.

Prolactin levels (ng/ml)	No	%
Mild (25-100)	85	96.59
Moderate (101-200)	3	3.40
High (201-1000)	0	0
Very High >1000	0	0
Total	88	100

In this study, the maximum number 85 (96.59%) of patients were in the mildly increased prolactin level group.

Table:- 5 Various clinical Presentation in hyper prolactinemic patients.

Symptoms	No	%
Menstrual disturbances		
-Oligomenorrhea	27	30.68
-Amenorrhea	21	23.86
-Menorrhagia	2	2.27
Other Symptoms		
-Galactorrhea	20	22.72
-Headache	1	1.13
-Hirsutism	1	1.13
-No symptoms	16	18.18
Total	88	100

In this study, the regular cycles were in 38(43.18%) patients. Oligomenorrhea, Amenorrhea and menorrhagia were present in 27 (30.68%), 21 (23.86%), and 2(2.27%) of patients. 20(22.72%) patients presented with complaint of galactorrhea. both amenorrhea and galactorrhea were seen in 19 (21.59%) of the patients.

In this study, the regular cycles were in 38(43.18%) patients. Oligomenorrhea, Amenorrhea and menorrhagia were present in 27 (30.68%), 21 (23.86%), and 2(2.27%).

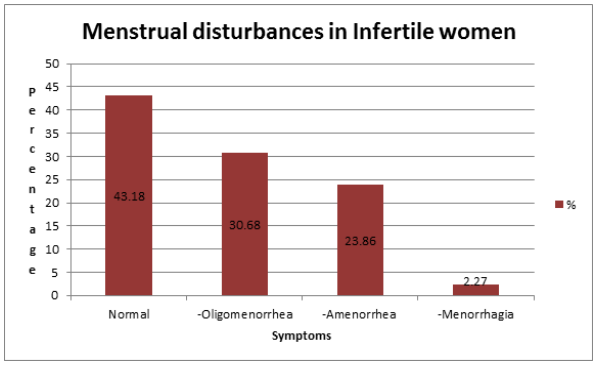

Figure 1: Menstrual disturbances in Infertile Women

Table:- 6 Presence of galactorrhea in the study group

Galactorrhea	No	%
Present	25	28.40
Absent	63	71.59
Total	88	100

In this study, galactorrhea was found in 25(28.40%) patients after clinical examinations

Table 7 Presence of Hypothyroidism in the study group

Hypothyroidism	No.	%
Present	13	14.77
Absent	75	85.22
Total	88	100

In this study, hypothyroidism was present in 13 (14.77%) patients.

All patients MRI could not be done As an MRI facility was not available in the town. history of drug-induced hyperprolactinemia was found in 6.81 % of patients. Polycystic ovarian disease was found in 5.68% of patients.

Medical treatment was given in all patients with cabergoline, The dose of cabergoline was .25mg biweekly. Normal prolactin level was achieved in 2-4 months in maximum patients. No sideeffects were observed during treatment.

DISCUSSION

Hyperprolactinemia refers to the consistent elevation of fasting serum prolactin more than 25ng/ml in the absence of pregnancy and puerperal lactation states. Patients with hyperprolactinemia present with ovulatory dysfunction and infertility, menstrual, disturbance, galactorrhea, delayed pubescence manifestation of polyendocrinopathy, or tumors designated as prolactinomas.

In this study, the maximum number 54 (61.36%) of patients were in 21-25 years of age group followed by 18(20.4%) in the 26-30 age group. In our study, the minimum age of hyperprolactinemia females and presentation is 15 year and the maximum age is presentation is 43 years. Our Study is comparable to the study ofAinaviIsah et al [10] in which the majority of the infertile females with hyperprolactinemia (58.6%) were aged 25-34 year and the minimum age of hyperprolactinemia females and presentation is 15 years and the maximum age of presentation is 44 year. In the study of Vane& Thornier [11]the, most of the patient were between 15 and 45 years of age.

In this study, the maximum number of patients 65 (73.86%) were of normal weight , 20 (22.72%) patients were overweight and only 3 (3.40%) were obese. In the study of Grimaldi F et al [12]higher prolactin level was found in the obese individual but in our study, there was no correlation was found with obesity. Our study was comparable to one another study in which 70% of patients were of normal weight,16% were overweight and 13% were obese.[13]In another study 12% ofpatients were overweight and only 3% were obese [14]. In the result of the study conducted by Priyanka Sharma et al[15]56.09% patients were normal weight and 43.9% were obese and overweight.

In this study, the maximum number of patients 60(68.18%)were of primary infertility. Our study is comparable with one another study in which primary infertilities were 60% and secondary infertilities were 40% [13]. The incidence of hyperprolactinemia was 60% in primary infertility and 22% in secondary infertility.In the study ofPriyanka Sharma[15]the incidence of hyperprolactinemia in primary infertility was 46% and secondary infertility was 40%.In study of Avasthik et al[16]the division was 60% and 40 % .It was43% and 21% in the study of Akhter and Hassan et al.[17]

In this study, the maximum number 85 (96.59%) of patients were in the mildly raised prolactin level group. Which is comparable to one another study, serum prolactin level was mildly raised in 96.8% of the patients and moderately raised in 3.2% of the patients[10]. Our finding was different from the finding of Randal et al [18]who found 61.8% of the patients to have moderately raised prolactin level and 39% of the patients had highly raised levels of prolactin.

In this study, the regular cycles were in38(43.18%) patients. Oligomenorrhea, Amenorrhea and menorrhagia were present in 27 (30.68%), 21 (23.86%), and 2(2.27%) of patients respectively.In the study of Priyanka Sharma[15]30% of patients complained of obesity, 17% patients complained of abnormal hair growth and menstrual complaints were 56%. Oligomenorrhea, Amenorrhea and menorrhagia were seen in 51%, 3% and 2% of the patients respectively. In the study of AvasthiK et al[16]regular cycles were in 42% ,Oligomenorrhea, Amenorrhea and menorrhagia were seen in 50%, 6% and 2% of the patients. Hirsutism was present in 14.4% of patients and headache in 45% of patient with hyperprolactinemia in the study of AHZargar[19]which was not comparable with our study.

In our study galactorrhea was found in 25(28.40%) patients after clinical examinations. Various studies showed galactorrhea in 26.31% , 18% and 25% of hyperprolactinemic patients[20,21,22].The incidence of galactorrhea varies among different studies and occurs in 30-80% of patients.[23,24]

In our study in only 14.77% of patients, hypothyroidism was found. Various studies showed the incidence of hypothyroidism in hyperprolactinemic patients were 18%, 8%, 20%, 20%.[20,25,26,27]

CONCLUSION

Prolactin may stop ovulation and cause amenorrhea, in less severe cases Intermittent ovulation or ovulation that takes a long time to occur causes infrequent or irregular periods. Anovulatory cycle, Luteal face defect and sex hormonal imbalance caused by hyperprolactinemia results in infertilitythat's why estimation of serum prolactin should be done at an early stage of an infertility workup. In our study, the prevalence of hyperprolactinemia and hypothyroidism was found very high which emphasize the importance of estimating TSH and Prolactin in infertility. In our study Oligomonorrhea, amenorrhea and galactorrhea are the commonest presentations in hyperprolactinemia. Proper Diagnosis and treatment results in an improvement in symptoms and an increase in conception rates in infertile patients.Dopamine Agonist restores normal ovarian function and is the first timetreatment for most patients wishing to conceive.

REFERENCES

1. Biller BM, Luciano A, Crosignani PG, Molitch M, olove D, Rebear R, et al. Guidelines for the diagnosis and treatment of hyperprolactinemia. J Reprod Med. 1999;44(Supp112):1075-84.Pubmed
2. Casenueva FF, molitch ME Schlechte JA Abs Bonert V, Bronstein MP et al

guideline of the pituitary society for the diagnosis and management of prolactinomas Clin endocrine 2006;65265-73
3. Molitch ME. drugs and prolactin pituitary 2008;11:209-18.
4. Luciano AA, the clinical presentation of hyperprolactinemia J Reporo med 1999;44:1085 90
5. Roger A. Lobo MD, David M. Gershenson MD, Gretchen M. Lentz MD, Fidel A Valea, MD; 7th edition; Comprehensive gynaecology; Hyperprolactinemia, galactorrhea and pituitary adenomas Page 853-864.
6. Webster J, Scanlin MF. Prolactinomas. In: Sheaves R, Jenkins PJ, Was JA, editors. Clinical Endocrine Oncology. Oxford: Blackwell Science; 1977. pp. 189-94.
7. Minakami H, Abe N, Oka N, Kimura K, Tamura T, Tamada T Prolactin release polycystic ovarian Syndrome. Endocrinol Jpn1988;35:303-10. Pubmed.
8. Kearns AE, Goff DC, Hayden DL, Daniels GH. Risperidone-associated hyperprolactinemia. EndocrPract. 2000;6:425-9. Pubmed.
9. Ferrari C, Paracchi A, Mattei AM, et al. Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta Endocrinol. 1992;126:489-494.
10. Idris AinaviIsah, Ibrahim Sambo Aliyo. Rasheed Yusuf, HS Isah, AJ Randawa, AG Adesiyun Hyperprolactinemia And female infertility: Pattern of clinical presentation in a tertiary.
11. Vance ML, Thorner MO. Prolactin: Hyperprolactinemic syndromes and management. In: DeGroot LJ, Besser M, Burger HG, (eds). Text Book of endocrinology. Philadelphia: W.B. Saunders Co., 1995. p. 394-401.
12. Grimandi F, Mazzolni A, PaternitiBarbino R, Torossi L, Proto g, F Bertolissi ; Changes in secretion of prolactin in obesity; Minerva Endocrinologica 01 OCT 1990 , 15 (4) : 267-271 . PMID 2129207
13. KalikiHymavathi, Surekha Tadisetti, DivyaPusarla, PrasunaPambadi; Correlation of serum thyroid hormones and prolactin levels to female infertility; international journal of Reproduction, Contraception, Obstetrics and GynaecologyHymavathi K et al. Int J Reprod Contracept Obstet Gynecol. 2016 Nov;5(11):4018-4024 www.ijrcog.org; DOI: http:// dx.doi.org/ 10.18203/2320-1770.ijrcog20163882
14. Bolumar F, Olsen J. European Body Mass index and Delayed Conception: A European Multicenter Study Of infertility and subfecundity. American Journal of Epidemiology. 2000;151:11.
15. Priyanka Sharma, Anita Pal, Rajeev Sood, Saroj Jaiswal, Suman Thakur, Anupam Sharma; Correlation of prolactin and thyroid disorders in infertile women; Internationa Journal of Reproduction, Contraception, Obstetrics and GynaecologySarma P et al. Int J Reprod Contracept Obstet Gynecol. 2017 Feb;6(2):649-653. www.ijrcog.org
16. Avasthi K, Kaur J, Gupta S, Narang P A. Hyperprolactinemia and its correlation with hypothyroidism in infertile women. J ObstetGencol India. 2006;56(1):68-71.
17. Akhter N, Hassan S. Sub-clinical hypothyroidism and hyperprolactinaemia in infertile women: Banglades perspective after universal salt iodination. Intern J Endocrinol. 2008;5(1).
18. Randall RV, Laws ER Jr., Abboud CF, Ebersold MJ, Kao PC, Scheithauer BW, et al. Transsphenoidal microsurgical treatment of prolactin-producing pituitary adenomas. Results in 100 patients. Mayo Clin Proc 1983;58:108-21.
19. AH Zargar, BA Laway, SR Masoodi, MH Bhat, AI Wani, MI Bashir, M Salahuddin*, R Rasool*; Clinical and Etiological Profile of Hyperprolactinemia - Data from a Tertiary Care Centre; Sahel medical journal; Hyperprolactinemia and female infertility: Pattern of clinical presentation in a tertiary health facility in Northern Nigeria
20. Shamali, Choudhary SD, Goswami A. Hyperprolactinemia and reproductive disorders-a profile from the northeast. J Assoc Physicians India 1995:43:617-8.
21. Kumkum A, Jasmine K, Shweta G, Pal Ajeshwar N. Hyperprolactinemia and its correlation with hypothyroidism in infertile women. J ObstetGynecol India. 2006;56(1):68–71. [Google Scholar]
22. Mishra R, Baveja R, Gupta V et al. Prolactin levels in infertility with menstrual irregularities. J ObstetGynecol India 2002; 52:40-3
23. Frank Ks, Nabarro JDN, Jacbos HS, prevalence and presentation of hyperprolactinemia in patients with functionless pituitary tumors. Lancet 1977;1:778-80
24. Thorner MO, Besser GM. Bromocriptine treatment of hyperprolactinemia hypogonadism. Acta Endocrine 1978;88(supp216):131-46
25. Goswami B, Patel S, Chatterjee M, Koner BC, Saxena A.: Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J ReprodInfertil, 2009; 10(3):207-212.
26. Sharma U R, Parmar C: Thyroid profile in infertile women and menstrual dysfunction. Source Indian Medical Gazette, updated 2007, www. endocrineindia.com/thyroidnewsite.
27. Manjusha D. Hivre, Dhananjay V. Bhale, Roshan K. Mahat, Ashlesh A. Bujurge; Study of Serum TSH and Prolactin levels in patients of Female infertility; International journal or Recent Trends in Science And Technology, ISSN 2277-2812 E ISSN 2249-8109, Volume 9, Issue 1, 2013 pp 144-145.