

A study on Hyperprolactinaemia and associated factors among women attending Gynecology outpatient department at a tertiary teaching hospital in West Bengal



Debajyoti Tapadar¹, Debjani Sen Gupta²

¹Professor and Head, Department of Gynaecology and Obstetrics, Jagannath Gupta Institute of Medical Sciences and Hospital, Budge Budge, Kolkata, West Bengal, India, ²Assistant Professor, Department of Community Medicine, Calcutta National Medical College Kolkata, West Bengal, India

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ABSTRACT

Background: Prolactin has multiple biological functions and hyperprolactinaemia is a common condition in clinical practice in both females and males. It has many etiologies and may present with variable symptoms to health care workers. **Aims and Objectives:** To study the various etiologies and clinical presentation of patients presenting with hyperprolactinaemia in a tertiary care medical college and hospital in West Bengal to aid in quick decision management. **Materials and Methods:** The current study was a cross-sectional study with follow up conducted over a period of one year in the Department of Gynecology and Obstetrics, Jagannath Gupta Institute of Medical College and Hospital. Following sample size calculation, a total of 1824 women were enrolled for the study of which 53 were found to have raised prolactin level (after following proper inclusion and exclusion criteria) They were subsequently further examined and followed up. **Results:** Majority of the subjects studied belonged to 20-29 age group (49.05%) followed by 30-39 years age group (35.85%). The most common cause of hyperprolactinaemia in our study were idiopathic (24.53%) followed by drugs (22.64%) and pituitary adenoma. Most of the patients with hyperprolactinaemia, presented with complain of infertility (56.6%), menstrual abnormality (50.94%) and galactorrhoea (18.87%) in our study. Therapeutic drugs used for various reasons were one of the main cause of hyperprolactinaemia (22.64%) and mainly due to use of proton pump inhibitor with prokinetics use. **Conclusion:** Hyperprolactinaemia is very much common in patients with infertility, menstrual abnormality or galactorrhoea and mostly are due to idiopathic or drug induced causes. With early initiation of treatment most of the causes and effects can be cured.

Keywords: Hyperprolactinaemia; Idiopathic Hyperprolactinaemia; Drug induced Hyperprolactinaemia; Infertility

INTRODUCTION

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. It is an essential factor for normal production of breast milk following childbirth. Furthermore, Prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and

follicle-stimulating hormone. An excess of prolactin, or hyperprolactinaemia, is a commonly encountered clinical condition.¹ It is the most common disorder of the hypothalamic-pituitary-axis. Patients typically present with hypogonadism, infertility or, in the case of macroadenomas, symptoms related to mass effect (headache and visual field defects). Management of this condition depends on the cause and on the effects, it has on the patient. Commonly

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Address for Correspondence:

Dr Debjani Sen Gupta, Assistant Professor, Department of Community Medicine, Calcutta National Medical College Kolkata, West Bengal
Mobile No: +91-9433357290. **E-mail ID:** drdebjanisg@gmail.com

cited indications for treatment of macroprolactinomas include infertility, hypogonadism, prevention of bone loss and bothersome galactorrhea.^{2,3} However, indications and modalities of treatment of hyperprolactinemia due to pituitary microadenomas are less well defined.²

An excess of prolactin above a reference laboratory's upper limits, or "biochemical hyperprolactinemia," can be identified in up to 10% of the population.¹ The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9-17% in women with reproductive diseases. Its prevalence was found to be 5% in a family planning clinic.⁴ Women with oligomenorrhoea, amenorrhoea, galactorrhea or infertility, and men with hypogonadism, impotence or infertility must have serum prolactin levels measured.¹ It is estimated at 9% among women with amenorrhoea, 17% among women with polycystic ovary syndrome, 25% among women with galactorrhea and as high as 70% among women with amenorrhoea and galactorrhea.² The prevalence is about 5% among men who present with impotence or infertility.¹

Prolactin is a 23 kDa polypeptide hormone (198 amino acids) synthesized in the lactotroph cells of the anterior pituitary gland. Its secretion is pulsatile and increases with sleep, stress, food ingestion, pregnancy, chest wall stimulation, and trauma. The main biological action of prolactin is inducing and maintaining lactation. However, it also exerts metabolic effects, takes part in reproductive mammary development and stimulates immune responsiveness.^{5,6}

There are a variety of causes which can lead to hyperprolactinaemia. These include physiological causes like pregnancy, lactation, exercise or sleep. The pathological causes are broadly divided into three causes. Conditions affecting pituitary gland like tumors, conditions damaging hypothalamic-pituitary stalk and systemic disorders can all lead to hyperprolactinaemia.⁷ Drug-induced causes are one of the most common etiologies of hyperprolactinaemia that we come across in day-to-day practice.

Identifying the correct etiology helps the clinician to give the best therapy minimizing unnecessary procedures and medication prescription.

Aims and objectives

This cross-sectional observational study was conducted with the following objectives

1. Enumerate the various causes leading to raised prolactin level in serum
2. Find out the presenting features of cases of prolactinaemia to aid quicker diagnostic and therapeutic measures.

MATERIALS AND METHODS

The current observational study was conducted at Jagannath Gupta Institute of Medical sciences, Budge Budge, West Bengal in the Gynecology out-patient department for 12 months.

The sample size was calculated considering a prevalence of hyperprolactinaemia of 5%⁴ sample size at confidence of 95%, power 80% and allowable error 15 % sample size was 1824.

Sampling method: Total enumeration of all cases with eligibility criteria (who attended Gynecology and Obstetrics outpatient department were enrolled for a period of one calendar year from January 2019 to December 2019 till a sample size of 1824 was reached. A total of 1824 cases were tested for prolactin level. Of which 53 women were found to have raised prolactin levels, who were further interviewed and investigated. The evaluation of hyperprolactinaemia was undertaken as per standard protocol. A detailed drug exposure history was also undertaken. Biochemical and hormonal evaluation and pituitary imaging (if required) were done. When no definite cause could be attributed the case was labeled as idiopathic. Written and informed consent was taken from each subject. The study was pre-approved by the Institutional Ethical Committee of this institution. The data was analyzed using standard statistical methods. The graphs and tables were generated using Microsoft Excel 2007 software.

Inclusion criteria: The subjects whose had raised levels of prolactin were enrolled in this study.

Exclusion criteria: Previously diagnosed cases, patients with known physiological causes of hyperprolactinaemia such as pregnancy, lactation or recent history of stress or surgery were excluded from the study along with infertility due to male factors.

RESULTS

Most of the patients with hyperprolactinaemia had values <50 microgram/L (77.35%) and only one patient (1.9%) had values >150 microgram/L (Table 1).

Table 2 shows the age wise distribution of study population where it is seen that range extends from 18 -48 years with 49.05% being in the age bracket of 20-29 years. The next age group of 30-39 years constituted 35.85% of study population.

In Table 3 it is presented that infertility accounts for most frequent complaints established by history

Table 1: Prolactin levels among study subjects

Prolactin Level (25microgm/L)	Number of Patients	%
<50 microgram/L	41	77.35
51-150 microgram/L	11	20.75
>150microgram/L	1	1.9

Table 2: Age-wise distribution of study population

Age	Number of Patients	%
<20	4	7.55
20-29	26	49.05
30-39	19	35.85
>40	4	7.55

Table 3: Distribution of common features of hyperprolactenemia among study subjects

Presentation	Present	Absent	Not Stated
Infertility	32 (60.38%)	6 (11.32%)	15 (28.30%)
Menstrual Disturbance	27 (50.94%)	23 (43.40%)	3 (5.66%)
Galactorrhea	10 (18.87%)	12 (22.63%)	31 (58.5%)
Headache	8 (15.09%)	8 (15.09%)	37 (69.81%)
Visual disturbances/other pressure symptoms	4 (7.55%)	11 (20.75%)	38 (71.7%)
Dyspareunia	5 (9.43%)	2 (3.77%)	46 (86.8%)
Breast Tenderness	2 (3.77%)	1(1.9%)	50 (94.34%)
Libido	1 (1.9%)	0	52 (98.1%)

(60.38%) followed by menstrual disturbance (50.94%) and galactorrhoea (18.87%). More than one presenting symptoms like infertility, menstrual disturbance was recorded from each subject. Headache was present in 15.09% of cases and visual disturbances due to pressure symptoms was seen in one case (7.55%).

Table 4 indicates the chief complaint which also supports the findings of Table 3 indicating infertility to be the most common presenting symptom at 56.6% followed by oligomenorrhoea, while heavy painful menstrual periods accounting for 7.54% cases.

Table 5 indicates that 58.49% of women have symptomatic duration of <6 months and sought treatment for infertility. Symptom duration of more than 6 to 12 months was seen in (26.41%) of subjects.

Table 6 elucidate the causes of hyperprolactinaemia in these patients. The cause was unknown or idiopathic in 13 patients (24.53%) followed by uses of medication which accounted for 12 cases (22.64%). Polycystic ovarian disease and Hypothyroidism were identified as the cause in 9 patients (16.98%) and in 8 patients (15.09%) respectively. Pituitary microadenomas was found in 10 patients mainly

Table 4: Clinical presentation of hyperprolactenemia among study subjects

Main Presentation	Number of Patients	%
Infertility	30	56.60
Oligomenorrhoea/Amenorrhoea	8	15.09
Heavy Painful Periods	4	7.54
Recurrent Miscarriage	2	3.77
Headache/Visual Problem	1	1.89
Galactorrhea	2	3.77
Galactorrhea/Dyspareunia	1	1.89
Infertility/Hot Flushes	1	1.89
Dyspareunia	1	1.89
Irregular Painful Periods	1	1.89
Headaches/Breast Soreness	2	3.77

Table 5: Duration of symptoms prior to diagnosis

Duration of Hyperprolactinaemia	Number of Patients	%
<6 Months/Transient	31	58.49
>6 Months -12 Months	14	26.41
>12 Months -24 Months	3	5.66
>24 Months-36 Months	5	9.43

Table 6: showing etiologies of hyperprolactinaemia among study population

Cause of Hyperprolactinaemia	Number of Patients	%
Idiopathic	13	24.53
Hypothyroidism	8	15.09
drugs	12	22.64
PCOS	9	16.98
Pituitary adenoma	10	18.87
Renal failure	1	1.89

presenting with pressure symptoms (18.87%). Only 1 patient was diagnosed with renal diseases.

In Table 7, the drugs associated hyperprolactinaemia in the study population. Among drugs causing hyperprolactinaemia, proton pump inhibitors (PPI)/H2 receptor blockers with or without prokinetics accounted for 46.15% of cases. Hyperprolactinaemia was seen in patients consuming antipsychotics/antidepressants in 30.77% of cases.

DISCUSSION

Hyperprolactinaemia is one of the most common endocrine disorders encountered in clinical practice. As discussed earlier, the cause could be as varied as pituitary tumors to drug-induced causes. The majority of women in this study presented with infertility, menstrual irregularity or other symptoms leading them to seek clinical help earlier.

Normal serum prolactin levels range from 5 and 25 microgram/Lt in females although physiological and diurnal

Table 7: Showing therapeutic drugs causing hyperprolactinaemia among study population

Drugs causing Hyperprolactinaemia	Number of Patients	%
Anti-psychotic/Anti-depressants	4	33.33
Anti -hypertensives	1	08.33
PPI with prokinetics	6	50
Contraceptives	1	08.33

variations occur.¹ As per the findings of the current study, most of the patients had values between 25 to 50 microgram/Lt.

The majority of population consisted of patients belonging to third decade (49.05%) according to our study which is similar to prevalence reported by Zargar et al.⁸ This could be due to the fact that majority of patients gets married in this age group and are therefore more bothered about their reproductive function and seek clinical help.

Infertility, Menstrual irregularity and galactorrhoea were the predominant symptoms among women with hyperprolactinaemia. The incidence of galactorrhoea in our study was 18.9% in comparison to prevalence of 45% by Zargar et al.,⁸ and 33% by Horng-Yih O et al.⁹ Similarly, we found menstrual irregularity to be present in 50.94% of women whereas Horng-Yih O et al.⁹ had reported similar problem in 42% of patients. The incidence of galactorrhoea in women with hyperprolactinaemia varies among different reports and occurs in 20-80% of subjects according to the study by Frank KS et al., (galactorrhoea uncommon) and by Thorner MO et al., (galactorrhoea 79% of cases).^{10,11} While galactorrhoea is the classic symptom of hyperprolactinaemia, it only occurs in less than half of such cases according to the study by Abha et al.¹²

However, majority of women in our study presented with Infertility either primary or secondary (60.38%). According to the study by Poppe K et al.,¹³ and Zollner U et al.,¹⁴ hyperprolactinaemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH (gonadotropin releasing hormone) and hence interfering with ovulation.^{13,14}

Menstrual abnormalities were detected in about 57.6% of the primary infertility cases in a study done by Goswami B et al.¹⁵ In our study also many patients, presented with infertility have menstrual problems (51%). Goswami B et al.,¹⁵ who found a higher occurrence of hyperprolactinaemia (41%) in the infertile women as compared to the controls (15%) in accordance with our study where majority patients with hyperprolactinaemia presented with infertility (60.38%).

Most of the patients according to our study 58.49% have duration < 6 months and mostly came for treatment of infertility, followed by those with duration of more than 6 to 12 months (26.41%).

Idiopathic cause is the most common cause of hyperprolactinaemia in our study (24.53%) followed by drugs (22.64%), pituitary microadenoma (18.87%), PCOS and hypothyroidism.

In a study conducted by Malik et al.,²³ to delineate the causes of increased prolactin levels, they reported the most common causes were prolactinomas (17%), transient hyperprolactinaemia (14.6%) and drug induced hyperprolactinaemia (14.4%). In the current study, transient hyperprolactinaemia due to idiopathic causes were the most common aetiology of hyperprolactinaemia and was diagnosed mostly in women being evaluated for infertility. Yet another study done by Ben-David M et al.,¹⁶ documented a transient rise of prolactin in females during their mid-cycle; the rate rises to 94% in those with infertility, ranging between 25–75 ng/mL and usually lasting for 1-3 days.

Drug-induced hyperprolactinaemia was the second most common cause of hyperprolactinaemia in our study where as it was also second most common cause reported by Horng-Yih O et al.,⁹ and Suliman et al.¹⁷ The most common drugs included Proton pump inhibitors (PPIs) and prokinetics in our study which is in good agreement with the study reported by Horng-Yih O et al.⁹

According to study conducted by Vilar L et al.¹⁸ PCOS is a common disorder in young adults and contributes to 13-16% of all cases of hyperprolactinaemia which is similar to our study where hyperprolactinaemia due to PCOS contribute 16.98%.

Fifteen percent of our patients also showed features of hypothyroidism. Some patients with primary hypothyroidism had moderate hyperprolactinemia.^{19,20} Long-term or inadequately treated primary hypothyroidism can cause pituitary hyperplasia that may mimic a pituitary tumour. Hyperprolactinaemia and enlargement of the pituitary gland due to thyroid failure can be reversed by treatment with L-thyroxine.^{21,22}

Prolactin-secreting pituitary adenomas are relatively common cause of hyperprolactinaemia and account for 30-40% of all pituitary adenomas, nearly all of which are benign. Depending on its size, the adenoma itself may cause signs and symptoms, including visual field abnormalities, blurred vision, and headache. In our study 10 (18.87%) patients have been diagnosed as pituitary adenoma (by CT scan), of which one patient had severe visual problem with pituitary macroadenoma.

Medications inducing hyperprolactinaemia constituted 14% of all cases in the study conducted by Azhar A. Malik et al.,²³ where most patients were on antipsychotics

or anti-emetics. Vilar et al.,¹⁸ reported a similar rate (12%) in Brazil; however, the rate was much higher (45.9%) in Scotland with rising prevalence during the last years of the study.^{18,24} In our study also medication was the cause in almost 22% cases and mostly due to PPIs with anti-emetics and anti-psychotics. The exact PPIs brand name or trade name could not be elicited as patients had taken it without medical prescription. Among the antipsychotics/anti-depressants two patients were on Citalopram and one on Paroxetine and Amitriptyline each with >24months duration.

Usual treatment of hyperprolactinaemia were followed with cause directed therapy along with Cabergoline treatment.

CONCLUSION

Hyperprolactinaemia is very much common in patients with infertility, menstrual abnormality or galactorrhoea and mostly are due to idiopathic or drug induced causes. The cause of hyperprolactinaemia should always be thoroughly evaluated as treatment can prevent considerable morbidity associated with this state. Early diagnosis and effective treatment are quite rewarding.

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Authors Contribution:

DT - Research methodology and Manuscript writing; **DS** - Concept, Study design and Manuscript preparation.

Work attributed to:

Department of Gynaecology and Obstetrics, Jagannath Gupta Institute of Medical Sciences and Hospital, Budge Budge, Kolkata, West Bengal, India

Orcid ID:

Dr. Debajyoti Tapadar - <https://orcid.org/0000-0003-1983-9343>

Dr. Debjani Sem Gupta - <https://orcid.org/0000-0002-2026-2660>

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