

Prolactin Assays In Infertility with Menstrual Dysfunctions a Prospective Study

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ABSTRACT

Background: Basic gynaecological endocrinology has been of paramount significance in the investigative approach in cases of menstrual dysfunction with infertility. **Objective:** Aim of the study is serum prolactin assays in cases of infertile patients with menstrual dysfunction.

Material and Methods: A prospective case control study conducted over a period of 1 year. Reproductive age patients of 20 to 40 yrs were selected and categorized into two groups. **Control Group:** Comprised of 50 fertile women with normal menstrual cycles and fertility. **Study Group:** Comprised of 150 infertile women (primary or secondary) with menstrual dysfunctions. Detailed obstetrics history with relevant laboratory, radiological investigations including serum prolactin level was done.

Results: incidence of hyperprolactinaemia in our study was 24.6%. Incidence of hyperprolactinemia in different menstrual disorders in oligomenorrhoea was 27.27%. In secondary amenorrhoea 30.2%. Primary amenorrhoea 5.5%, polycystic ovarian disease 33.3%, irregular menstruation (9.09%), regular anovulatory cycles (25%) regular ovulatory cycles (40%). In our study in hyperprolactinemic patients, majority of patients presented with oligomenorrhoe (48.7%) as menstrual abnormality followed by secondary amenorrhoea (35.1%). In our study the mean serum prolactin level in patients with secondary amenorrhoea (111.42 ng/ml) was significantly higher than in patients with oligomenorrhoea (69.3 ng/ml) incidence of primary infertility in hyperprolactinemia cases was 75.67% and secondary infertility (27.07%). The test of proportion showed high significant difference between the two ($p < 0.01$). In our study, incidence of hyperprolactinemia in patients with galactorrhoea was (66.6%) high significant difference ($p < 0.01$) was observed between serum prolactin levels of cases with galactorrhoea and without galactorrhoea. galactorrhoea was not a constant feature only 13.5% of hyperprolactinaemic patients had demonstrable galactorrhoea.

Conclusion: Hyperprolactinemia is quite an important cause of infertility and menstrual dysfunction, hence serum prolactin estimation is mandatory for diagnosis.

Keywords: Hyperprolactinemia Galactorrhoea Infertility.

INTRODUCTION

classification and determination of infertility in females have been based on various investigative procedures such as clinical evaluation, endometrial biopsies, endocrine studies, sonography, hysterosalpingography, hysteroscopy, laparoscopy, others. Menstrual dysfunction

with infertility is a distinct clinical entity due to derangement in hypothalamo-pituitary ovarian-uterine axis there by resulting in absence or irregular menstruation for a variable period. but to locate the site of dysfunction and as well as to search for the cause of the disorder has been a matter of great concern for the clinicians. Knowledge of the basic gynaecological endocrinology has been of paramount significance in the investigative approach in cases of menstrual dysfunction with infertility. Thus the role of endocrinological evaluation by radioimmunoassay appears a sound answer for evaluation. Recent advances in reproductive endocrinology has incriminated the anterior pituitary polypeptide hormone prolactin in the pathogenesis of anovulation in amenorrhoea galactorrhoea syndrome and other menstrual dysfunctions with infertility. Prolactin is a polypeptide hormone with 198 aminoacids it is secreted by the pituitary lactotrophs which coexist with G.H. producing cells located in the lateral wings of the pituitary glands.^[1] The primary regulation of prolactin secretion is mediated through hypothalamic inhibition, and the diagnosis of hyperprolactinemia can be established without the use of stimulation or suppression tests.^[2] Hyperprolactinemia is a well-established cause of hypogonadotropic hypogonadism. PRL acts on kisspeptin-1 neurons expressing the PRL receptor (PRL-R) and is responsible for decreased kisspeptin-1 and GnRH secretion, leading to anovulation, It adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation.^[3] It may be seen in menstrual and ovulatory dysfunction like anovulation, amenorrhoea and galactorrhoea. Determination of prolactin is used as a functional check on the regulatory mechanism between the hypothalamus, the pituitary and gonads.^[4] so the Aim of the study is serum prolactin assays in cases of primary and secondary infertility with menstrual dysfunctions.

MATERIAL & METHODS

Present study was a prospective case control study conducted in the department of obstetrics and gynaecology of MLB Medical College, over a period of 1 year. Patients were selected from the outpatient department and ward of hospital. Reproductive age patients of 20 to 40 years were selected and categorized into two groups. **Control Group:** comprised of 50 fertile women with normal menstrual cycles and fertility. **Study Group:** comprised of 150 infertile women with infertility (primary or secondary) with menstrual dysfunction in the form of amenorrhoea primary or secondary, oligomenorrhoea, menorrhagia, irregular menstrual cycle, regular anovulatory cycle, galactorrhoea, polycystic ovarian disease.

Inclusion Criteria: female in age group 20 to 40 years, infertility (primary or secondary) with menstrual dysfunction.

Exclusion Criteria: were subjects with age <20 or >40 years, male factor infertility, amongst female factors tubal factors, any congenital anomaly of urogenital tract or any obvious organic lesion, women with diagnosed hyperprolactinemia or thyroid abnormality, tuberculosis and women with history of anxiety disorders and other psychological disorders and on drug treatment for the same. Written informed consent was taken from the participants recruited in the study. Ethics committee approval was taken at the outset. Those fulfilling inclusion criteria and who did not have any exclusion criteria were recruited and Detailed obstetrics history with relevant laboratory, radiological investigations including serum prolactin level was done. Relevant samples of all the participants were subjected. Diurnal variation on serum prolactin level was minimized by taking early morning sample at fixed hours of 8 a.m. to 9 a.m. participants were instructed for nil per-orally from the night before and avoid stimulation of breast nipple and intercourse. As prolactin levels vary with physical examination (nipple stimulation, intercourse, breast examination). Serum prolactin level of the participants was recorded which was assayed by competitive enzyme linked immunosorbent assay (ELISA) using commercially available kit (accubind ELISA micro wells

This study included 150 cases and 50 control subjects. Incidence of serum prolactin was studied in different groups and compared. Observed results are mentioned in various.

RESULTS

This study included 150 cases and 50 control subjects. incidence of serum prolactin was studied in different groups and compared. Observed results are mentioned in various table forms.

Table 1: showing distribution of subjects in various groups table forms

	No. of cases	Percentage
Cases		
1. Primary infertility	102	68%
2. Secondary infertility	48	32%
Control	50	-
Total	200	100

Table 1. Shows the distribution of cases in study and control groups. Total number of primary infertility cases were 102 & secondary infertility cases were 48 Cases in control group were 50 only.

Table 2: Showing distribution of infertile patients (Primary or Secondary) with various menstrual dysfunctions

group	Different group of infertile patients	Total No of cases	% of cases	Primary infertility	Secondary Infertility
	Without Galactorrhoea	141			
	1.oligomenorrhoea	60	40.0	46	14
	2.secondary amenorrhoea	40	26.6	18	22
A	3.Primary amenorrhoea	18	12.0	18	-
	4.PCOD	3	2.0	3	-
	5.Irregular Menses	11	7.3	6	5
	6.Regular Anovulatory cycles	4	2.6	3	1
	7.Regular ovulatory cycles	5	3.3	4	1
	With Galactorrhoea	9	6		
	1.oligomenorrhoea	4	2.6	2	2
B	2.secondary amenorrhoea	5	3.3	2	3
	3.Primary amenorrhoea	-	-	-	-

	5.Irregular Menses	-	-	-	-
	6.Regular Anovulatory cycles	-	-	-	-
	7.Regular ovulatory cycles	-	-	-	-
total		150		102	48

Table 2: revealed distribution of cases in 2 groups. **GROUP A**; infertile patients without galactorrhoea and with menstrual dysfunctions. **GROUP B**: infertile patients with galactorrhoea and with menstrual dysfunctions .observations tabulated.

Table 3: Showing the level of Prolactin in control group

No of cases	Range of Prolactin level in ng/ml	Mean +_SD
50	5.5 -22.0	14.62+_4.31

Table 3: Shows level of prolactin in control group. Lower limit was 5.5ng/ml and maximum level was 22.ng/ml. mean value was 14.62+_4.31ng/ml

Table 4: Showing the prolactin concentration in different groups of infertile patients and incidence of hyperprolactinaemia.

Different groups	No of cases	Prolactin range in ng/ml	Mean +_SD	Hyperprolactinaemia	
				cases	Percentage %
A.Without Galactorrhoea	141				
1.oligomenorrhoea	60	5-105.	29.92+_23.95	14	23.34
2.Secondary amenorrhoea	40	7.5-180	39.63+_43.81	11	27.5
3.primary amenorrhoea	18	8.5-90	20.07+_17.77	1	5.5
4.PCOD	3	22-35.5	27.34+_7.18	1	33.33
5.Irregular Menstruation	11	12 -90	25.67+_21.56	1	9.09
6.Regular anovulatory cycles	4	16.5-362	10.50+_13.08	1	25
7.Regular ovulatory cycles	5	5.5-60.5	29.90+_23.33	2	40
B With Galactorrhoea	9			6	66.66
1.oligomenorrhoea	6	20.5-385.0	107.94+_113.14	4	66.66

2. Secondary amenorrhoea	3	8.5-90	20.07+_17.77	2	66.66
Total	150			37	24.66%

Table 4: Showed that out of 150 infertile cases, hyperprolactinemia was present in 37 cases i.e , (24.66%).Majority of the cases of hyperprolactinaemia, were present in infertile cases with galactorrhoea(66.6%) .In cases without galactorrhoea, majority of the cases of hyperprolactinaemia were present in infertile cases with regular ovulatory cycles(40%),followed by (33.3%)in cases with PCOD,(27.5%)in cases of secondary amenorrhoea and the minimum (5.5%)in cases with primary amenorrhoea

Table 5: Showing the menstrual pattern and serum prolactin level in Hyperprolactinaemia.

Menstrual pattern	Mean serum prolactinng/ml	No of patients (N=37)	Percentage%
1.oligomenorrhoea	69.35	18	48.7
2.Secondary amenorrhoea	111.52	13	35.1
3.primary amenorrhoea	90	1	2.7
4.PCOD	35.5	1	2.7
5.Irregular Menstruation	90	1	2.7
6.Regular anovulatory cycles	362	1	2.7
7.Regular ovulatory cycles	58.25	2	5.4

Table 5: Revealed majority of hyperprolactinemia patients have menstrual dysfunction as oligomenorrhoea(48.7%),followed by secondary amenorrhoea(35.1%).Mean serum prolactin level in patients with secondary amenorrhoea (111.52ng/ml)was highly significant (p<0.001) then that in patients with oligomenorrhoea (69.35ng/m).In regular anovulatory cycles, only one patient had higher prolactin level(362ng/ml).

Table 6: Showing the incidence of infertility in hyperprolactinemia

Infertility cases	Number of cases with hyperprolactinaemia	Percentage of cases with hyperprolactinaemia
Primary infertilitycases	28	75.67%
Secondary Infertility	10	27.07%
total	37	100

Table 6.:showed majority of infertility cases in hyperprolactinemia cases were of primary infertility (75.67 %).Incidence of secondary infertility was (27.07%).The test of proportion showed high significant difference between the two(p<0.01).

Table 7: Showing the incidence of galactorrhoea in hyperprolactinaemic infertile cases

No of cases having hyperprolactinaemia	Cases with Galactorrhoea		Cases without Galactorrhoea	
	No	%	No	%
37	5	13.51%	32	86.4%
mean serum prolactin level (ng/ml)	135.96		83.6	

Table 7: Observed incidence of galactorrhoea was 13.5% in hyperprolactinemic infertile cases. Galactorrhoea was not a constant feature in hyperprolactinaemia patients. High significant difference ($p < 0.01$) was observed between mean serum prolactin levels of cases with galactorrhoea and without galactorrhoea.

DISCUSSION

The present study was carried out to find out the incidence of hyperprolactinaemia in infertility with different menstrual disorders, and serum prolactin assays in primary and secondary sterility with or without galactorrhoea.

The present study includes 150 cases in study and 50 in control group, out of 150 cases, there were 102 (68%) cases of primary and 48 (32%) cases of secondary infertility, similar to many studies.^[7,8] Madhuprita et al reported (65%) cases of primary infertility & (35%) cases of secondary infertility. Control group cases have normal fertility and normal menstrual cycles. Age of control group was 20 to 40 yrs. majority of primary infertility (50%) and secondary infertility (48.9%) cases belonged to age group of 26-30 yrs in our study, similar finding seen by Isah IA et al^[20] majority of the infertile females with hyperprolactinemia (58.6%) were aged 25–34 years. This finding suggests that most infertile females with hyperprolactinemia were in their mid-reproductive age

Level of serum prolactin in control group was 5.5-22 ng/ml and mean level was 14.62 ± 4.31 .^[7,20]

Incidence of hyperprolactinemia in our study was 24.66% consistent with many other studies.^[5,6,7,8,10] Mishra et al. have reported an incidence of 20% i It was 11.5% in study of Madhuprita et al. it is therefore possible to affirm that the subjective response of female reproductive axis shows a larger degree of sensitivity to hyperprolactinemia, so measurement of prolactin is mandatory in menstrual dysfunctions & infertility for correct diagnosis.^[5,6]

In our study hyperprolactinemia was present in 27.27% patients with oligomenorrhoea, 30.2% patients with secondary amenorrhoea, 5.5% patients with primary amenorrhoea, 33.3% in patients with polycystic ovarian disease, consistent with other studies (Jayesh J Sheth 1992), since chronic anovulation and disordered LH-FSH secretion appear to be the basic feature of PCOD, it is likely that endorphin liberation in the hypothalamus suppresses both dopamine and GnRH pathways leading to hyperprolactinaemia.

Hyperprolactinemia was present in 9.09% patients with irregular menstruation, 25% in patients with regular anovulatory cycles. Similar results seen in many studies.^[7]

Hyperprolactinemia has been proposed to block ovulation through inhibition of GnRH release. Kisspeptin neurons, which express prolactin receptors, were recently identified as major regulators of GnRH neurons^[12] the main cause of anovulation is impaired gonadotropin pulsatility and derangement of the estrogen-positive feedback effect on LH secretion in hyperprolactinemic patient. Idiopathic hyperprolactinemia in normally menstruating women with ultrasonographically documented ovulation was seen in 40% patients in our study, similar to many other studies. Thus we conclude that all patients with sterility irrespective of menstrual disorders or ovulation should be screened for prolactin estimation.

in our study out of 37 patients with hyperprolactinemia, majority of patients presented with oligomenorrhoea 48.7% as menstrual abnormality followed by secondary amenorrhoea 35.1%^[6,7] this is because increase prolactin levels produce anovulation and it prevents the LH pulsatility and interferes with the positive feedback action of estradiol at the hypothalamic level through the blockage of estrogenic receptors.^[13,14,15] There are reports that Pulsatile secretion of LH is also disturbed in normoprolactinemic hypothalamic amenorrhea. However, derangement of the estrogen-positive feedback effect on LH release is peculiar to hyperprolactinemia.^[13,14,15] 8.1% of patients with hyperprolactinemia had regular menstruation, regular ovulatory cycles were seen in 5.4% of patients.

In our study the mean serum prolactin level in patients with secondary amenorrhoea (111.52ng/ml) was significantly higher than in patients with oligomenorrhoea (69.35ng/ml), primary amenorrhoea (90ng/ml) and irregular menstruation (90ng/ml), these findings suggest that higher is the prolactin level more significant will be menstrual disturbance.

In our study, incidence of hyperprolactinemia, in patients with galactorrhoea was 66.6%. serum prolactin levels was significantly raised (135.96ng/ml) similar findings in many other studies. Galactorrhoea was not a constant feature in hyperprolactinaemic patient's. Our finding was that only 13.5% of patients had demonstrable galactorrhoea, similar incidence 16.22%. was reported in studies by Sharma et al^[7], and 20% by Mishra et al.^[5]

CONCLUSION

Major conclusions drawn from our study are .majority of primary infertility (49.08%) and secondary infertility cases (47.9%) belonged to age group of 26 to 30 yrs.

Incidence of hyperprolactinaemia in our study was 24.6%.^[10]

incidence of hyperprolactinemia in different menstrual disorders observed was ,in patients with oligomenorrhoea 27.27%. in secondary amenorrhoea 30.2%. primary amenorrhoea 5.5%, in patients with polycystic ovarian disease 33.3%, in patients with irregular menstruation (9.09%), in patients with regular anovulatory cycles (25%) in patients with regular ovulatory cycles (40%).

in our study majority of infertility cases were of primary infertility (75.67%) in hyperprolactinemia cases. Incidence of secondary infertility was (27.07%). The test of proportion showed high significant difference between the two ($p < 0.01$) The mean serum prolactin level in primary infertility participants was [15.18±8.485 ng/ml] while that in secondary infertility was [19.21±15.1 ng/ml] which shows that females suffering from secondary infertility had higher levels of serum prolactin level.^[9,11] similar to study of Badesara S et al, However, Akhter et al reported the mean prolactin level in primary infertility (495±340 nmol/l) to be higher than in secondary infertility (340±310 nmol/l).

In our study in hyperprolactinemic patients majority of patients presented with oligomenorrhoe (48.7%) as menstrual abnormality followed by secondary amenorrhoea (35.1%).

In our study the mean serum prolactin level in patients with secondary amenorrhoea (111.42ng/ml) was significantly higher than in patients with oligomenorrhoea (69.35ng/ml), primary amenorrhoea (90ng/ml) and irregular menstruation (90ng/ml) finding suggesting a higher is the prolactin level more significant will be menstrual disturbance.

In our study, incidence of hyperprolactinemia in patients with galactorrhoea was (66.6%) serum prolactin levels was significantly raised (132.96ng/ml) in these cases.

Galactorrhoea was not a constant feature in hyperprolactinaemic patients .in our study only 13.5% of hyperprolactinaemic patients had demonstrable galactorrhoea.

Hyperprolactinemia is quite an important cause of infertility and menstrual dysfunction. Galactorrhoea, its typical clinical marker is not present in all patients hence serum prolactin estimation is mandatory for diagnosis.

REFERENCES

1. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: Structure, function, and regulation of secretion. *Physiol Rev.* 2000;80:1523–631. [PubMed]
2. Chahal J, Schlechte J. Hyperprolactinemia. *Pituitary.* 2008;11:141–6. [PubMed] [Google Scholar]
3. Poppe K, Velkeniers B. Thyroid and Infertility. *Vertin K Acad Geneeskde Belg* 2002;64:389-99.

4. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Endocrine Society. Diagnosis and treatment of hyperprolactinemia: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96:273–88. [PubMed] [Google Scholar]
5. Mishra R, Baveja R, Gupta V, et al. Prolactin level in infertility with menstrual irregularities. *J Obstet Gynaecol India* 2002;52:40-3.
6. Rutstein, Shea O, Iqbal H Shah, 2004. Infecundity, Infertility and Childlessness in Developing Countries. DHS Comparative Reports No. 9. Calverton, Maryland, USA: ORC Macro and the World Health Organization.
7. Sharma S, Chaudhary V, Kharakwal S, et al. Serum prolactin assay: an important screening method in primary and secondary infertility in female. *J. Evolution Med. Dent. Sci.* 2016;5(16):766-768, DOI: 10.14260/jemds/2016/178
8. Madhuprita, et al. Prevalence of hyperprolactinemia in infertile cases and its correlation with TSH in a rural setup hospital. *Int J Reprod Contracept Obstet Gynaecol* 2013;2(4):626-630
9. Badesara S, Jakhar K. A crosssectional study to find the prevalence of hyperprolactinemia in infertile euthyroid patients in a hospital. *Int J Reprod Contracept Obstet Gynecol* 2020;9:4394-7
10. Sharma P, Prasad S, Tangri N. Female infertility and its correlation with serum prolactin and TSH concentration- an unmatched case control study. *J Pharm Biomed Sci.* 2013;30(30):902-7.
11. Akhter N, Hassan S. Sub-clinical hypothyroidism and hyperprolactinemia in infertile women: Bangladesh persepective after universal salt iodination. *Int J Endocrinol.* 2008;5:1-8. Cite this article as: Badesara S, Jakhar K.
12. Matsuzaki T, Azuma K, Irahara M, Yasui T, Aono T. Mechanism of anovulation in hyperprolactinemic amenorrhoea determined by pulsatile gonadotropin-releasing hormone injection combined with human chorionic gonadotropin. *Fertil Steril.* 1994;62(6):1143–1149. [PubMed] [Google Scholar]
13. Sonigo C, et al. Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration. *J Clin Invest.* 2012;122(10):3791–3795. [PMC free article] [PubMed] [Google Scholar]
14. rass MR, Shaw RW, Butt WR, Logan Edwards R, LondonDR. An abnormality of oestrogen feedback in amenorrhoea-galactorrhoea. *Br Med J* 1975;3:274-5
15. Baird DT, McNeilly AS, Sawers RS, Sharpe RM. Failure of estrogen-induced discharge of luteinizing hormone in lactating women. *J Clin Endocrinol Metab* 1979;49:500-6. *J Clin Invest.* 2012;122(10):3467–3468. doi:10.1172/JCI64455.
16. Avasti kumkum,kaur jasmine,Gupta Shweta. Hyperprolactinemia and its correlation with hypothyroidism in infertile women *J obstet gynecol India.* 2006;56:68-71.
17. Eldin S, Abdelghani A, Elmagadum A. Hyperprolactinemia as a cause of female infertility and its prevalence in central Sudan. *Egypt Acad. J.Biolog. Sci.* 2013;5(1):31-6.
18. Nallusamy S, Gracelyn LJ. Prevalence of hyperprolactinemia in infertile women and its association with hypothyroidism. *Int J Adv Med.* 2016;3(1):33-8.
19. Isah IA, Aliyu IS, Yusuf R, Isah H S, Randawa A J, Adesiyun A G. Hyperprolactinemia and female infertility: Pattern of clinical presentation in a tertiary health facility in Northern Nigeria. *Sahel Med J* 2018;21:1-5.