

A Study of Prolactin Levels in Infertile Women

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Abstract: Hyperprolactinemia is a common problem encountered in reproductive disorders and the most effectively treatable cause of endocrine infertility. It is a prospective study carried out in the department of OBG over a period of 14 months. The study group comprised of 100 cases of infertility and their complete history regarding mean age, BMI, Galactorrhea, menstrual irregularities was taken. Their prolactin levels and thyroid levels are taken and compared. The correlation between hyperprolactinemia and obesity, incidence of galactorrhea, menstrual irregularities, hyperthyroidism was found to be significant. So we concluded measurement of prolactin levels and TSH screening are important in all women who are not ovulating normally.

Key Words: Prolactin, Infertility, Galactorrhea, BMI; Hypothyroidism, Menstrual irregularities.

I. Introduction

Hyperprolactinemia is a common problem encountered in reproductive disorders. The understanding that prolactin hypersecretion not only causes galactorrhea and amenorrhea but also gonadal dysfunction and infertility led to the wider use of prolactin estimations.

Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhea, oligomenorrhea, anovulation, ovulatory cycles with short or inadequate luteal phase, and galactorrhea. Approximately two thirds of women having both galactorrhea and amenorrhea will have hyperprolactinemia. Of that group, approximately one third will have a pituitary adenoma. Estimation of serum prolactin levels is recommended in women with unexplained infertility, any menstrual irregularity with or without hirsutism, galactorrhea with or without amenorrhea, luteal phase defects, anovulation, anovulatory bleeding, and delayed puberty. Apart from these groups of women, infertile women with regular menses also may have hyperprolactinemia. With the determination of serum prolactin levels, greater attention is now being directed to the clinical and laboratory evaluation of hyperprolactinemic women. Some of the women with galactorrhea and hyperprolactinemia might have primary hypothyroidism. This disease is characterized by low serum level of thyroxine (T₄) and decreased negative feedback on the hypothalamopituitary axis. The resulting increased secretion of thyrotropin releasing hormone (TRH) stimulates thyrotrophs and lactotrophs, thereby increasing the levels of both thyroid stimulating hormone (TSH) and prolactin. The aims of the study were to find the incidence of hyperprolactinemia in female infertility after exclusion of male factor infertility, and to study its correlation with hypothyroidism and various symptoms of hyperprolactinemia.

Hyperprolactinemia is a frequently encountered and most effectively treated cause of endocrine infertility. Out of the 30.4% infertile female partners with endocrine disorders, 35.16% ie., every third patient had hyperprolactinemia. Hence prolactin determinations are essential in all infertile women.

Aim: The aim of the study is to evaluate the incidence of abnormal prolactin levels in infertile woman and to study its relation with various symptomatology.

II. Objectives of the Study

a) In the Present Study:

Hundred women with the Chief Complaint of infertility were taken as cases and their prolactin levels were studied along with other investigations for infertility. The study was performed for a period of 14 months.

b) Various aspects that are Stressed are:

Relationship between abnormal prolactin levels and various factors like

- i) Age
- ii) parity
- iii) Thyroid Status
- iv) Body Mass Index
- v) Menstrual Irregularities

vi) Galactorrhea

III. Material And Methods

This was a prospective study carried out in the Department of Gynaecology, King George Hospital, Andhra Medical college, Visakhapatnam, over a period of 14 months. The study group comprised of 100 cases of infertility (both primary and secondary). These 100 cases were subjected to serum prolactin estimation and detailed work up.

The complete history of all the patients regarding their marital status, duration and type of infertility, menstrual pattern, especially the presence of any irregularity, Body Mass Index, any history of drug intake including oral contraceptives was recorded. History regarding galactorrhea, thyroid dysfunction and visual disturbances was recorded.

The patients following thorough examination were subjected for the investigations including serum PRL. The values of prolactin above 25ng/ml were taken as hyperprolactinemic(Novak).

The data obtained, was evaluated by Chi-square and Standard Error of Proportion.

In hundred parous women, with normal menstrual cycles (26 to 30 days), 20 to 30 years of age, non-lactating for at least one year and not ingesting drugs, only serum prolactin levels were estimated to compare the significance of Hyperprolactinemia in infertile women and fertile women.

III. Method

For prolactin estimation, a fasting midmorning venous sample in follicular phase was taken. Blood was allowed to clot for 30 minutes and serum separated using REMI centrifuge and the levels determined by using the kit provided by DIA METRA s.r.l.. The specimen was stored at 2-80C for a short time (maximum two days). After incubation, the bound/free separation was performed by a simple solid phase washing and then the chromogen solution (TMB) was added. The absorbance was determined after an appropriate time needed for and the completion of enzyme reaction maximum color development. The prolactin concentration in the sample was calculated based on a series of standards. The color intensity is proportional to the prolactin concentration in the sample. The normal range taken was 2 -25 ng/mL. Serum TSH levels were measured when prolactin levels were >25.0 ng/mL using autoanalyzer. Women with serum prolactin levels > 100 ng/mL were advised CT scan or MRI.

IV. Results

In the present study out of 100 infertile woman, 62% belonged to primary infertility and 38% belonged to secondary infertility. Of these 51.6 % of primary infertile women were in 21-25 yrs age group, where as 47.36 % of secondary infertile women were in 25-30 yrs age group.

In the present study there were 11 cases of Hyperprolactinemia out of 100 infertile women. Among the hyperprolactinemic group, maximum number of both primary and secondary infertility cases had S.prolactin < 100 ng/ml, Only 4 cases of infertility were found to have values more than 100 ng/ml.

These patients had CT Brain - Reports were Normal.

Incidence of hyperprolactinemia in secondary infertility group was only 8% compared to 12.9% of primary infertility group.

This increase in prolactin levels in primary infertility compared to incidence in secondary infertility was statistically significant as the Z value was 0.81 falling within the range of -1.96 to + 1.96.(95% confidence limit) Level of freedom was (C-1)(R-1).

Mean Prolactin Level was 74.74 ng/ml in Hyperprolactinemic infertile women.

Hyperprolactinemia And Its Relation With Various Parameters

I. Relation With Age:

Out of 11 hyperprolactinemic women 27% were more than 30 years and 73% less than 30 years. In the 89 normoprolactinemic group only 6% were more than 30 years.

Most of the patients out of 100 were less than 30 years (92%) in both primary and secondary infertility cases.

The 8% of patients above 30 years had nearly 37.5% incidence of hyperprolactinemia when compared with 92 % of patients less than 30 years with 8.7% incidence of hyperprolactinemia.

This increase in prolactin levels with age was statistically significant as the standard error of proportion (Z value) was 1.54 falling within the range of -1.96 to + 1.96.

Level of freedom was (C-1)(R-1).

Table Showing Age & Prolactin Levels

Age in years	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
≤ 30	84 (94)	8 (73)	92
> 30	5 (6)	3 (27)	08
	89	11	100

II Relation With Obesity:

In this study, < 25 Kg/mt sq BMI was taken as Normal, 2: 25 Kg/mt sq BMI as overweight (Novak) ..

Table Showing Relation Between Obesity & Hyperprolactenemia

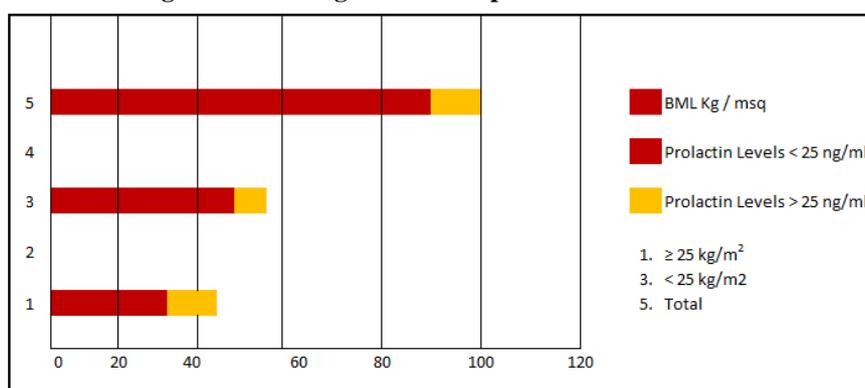
BMIkg/msq	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
≥ 25 Elevated	35 (39)	7 (64)	42
<25 Normal	54 (61)	4 (36)	58
	89	11	100

In the 11 hyperprolactinemic women, 7(64%) were <25 BMI and 4(36%) were >25 BMI.

Where as in the 89 normoprolactenemic women 54(61%) were <25 and 35(39%) were >25BMI.

- 16.6% of Infertile women with BMI > 25, were hyperprolactinemic when compared to 6.896% in women with BMI < 25.
- This was statistically significant as the standard error of proportion (Z value) was 1.62 with in the range of -1.96 to 1.96 .level of freedom (c-1) (r-1).

Figure -: Bar Diagrammatic representation of Table



11. Relation with Menstrual Irregularities:

Table Showing Relation Between Menstrual Irregularities & Hyperprolactinemia

Menstrual Irregularities	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
Present	28 (31.4)	09 (81.8)	37
Absent	61 (68.6)	02 (18.18)	63
	89	11	100

9 out of 11 hyperprolactinemic i.e., 81.8% presented with menstrual irregularities compared to 28 out of 89 i.e.,31.4% in women with normal prolactin.

24.3 % out of 37 Infertile women with menstrual irregularities had hyperprolactinemia when compared to 3.17% in 63 infertile women without menstrual irregularities.

This difference in the incidence of menstrual irregularities in infertile women with and without hyperprolactinemia was statistically significant.

Chi-square value after Yates correction was 10.66(p<0.01).

Anything more than 3.84 is significant (i.e $p < 0.05$)

IV. Relation With Galactorrhea

Table Showing Relation Between Galactorrhea & Hyperprolactinemia

Galactorrhea	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
Present	02 (2.25)	03 (27.27)	05
Absent	87 (97.75)	08 (72.72)	95
	89	11	100

There were 2 patients with galactorrhea and normal prolactin levels. They were both parous, and lactated their child till year back.

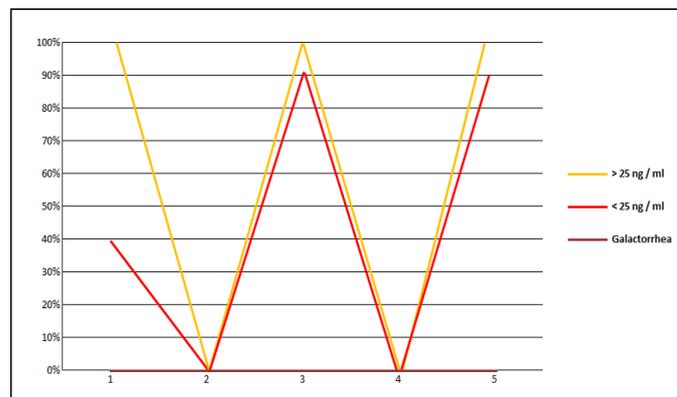
Out of 11 hyperprolactinemic women, 3 i.e., 27.27% were having galactorrhea where as only 2.25% i.e., 2 out of 89 with normal prolactin levels had galactorrhea.

From the data obtained, 60 % of 5 Infertile women with galactorrhea had hyperprolactinemia when compared to 8.42% of 95 infertile women without galactorrhea.

This difference in the incidence of galactorrhea in infertile women with and without hyperprolactinemia was statistically significant.

Z Value obtained was -1.85 lying within the range of -1.96 to +1.96 (standard error of proportion). Level of freedom was (c-1) (r-1)..

Figure - : Line Diagrammatic representation of Table



V. Relation With Both Galactorrhea And Menstrual Irregularities

Table Showing Relation Between Both Galactorrhea, Menstrual Irregularities & Hyperprolactinemia

Galactorrhea & Menstrual	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
Present	01 (1.12)	03 (27)	04
Absent	87 (97.75)	08 (72.72)	95
	89	11	100

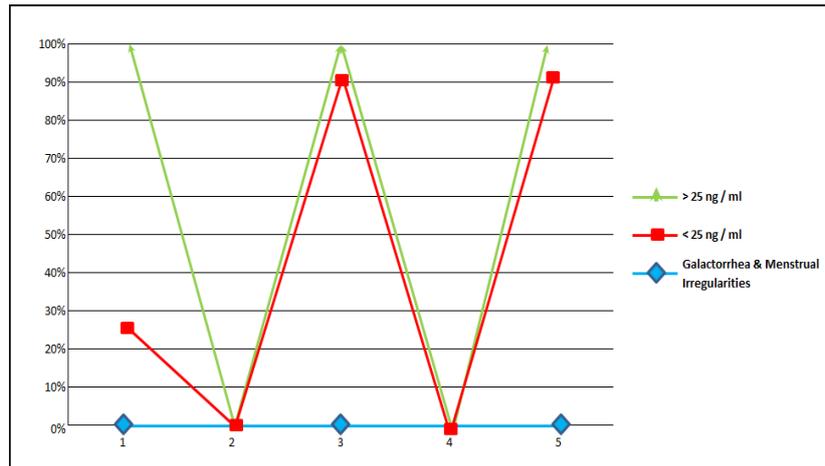
27% i.e., 3 out of 11 hyperprolactinemic infertile women were having both the symptoms compared to 1.12% i.e., 1 out of 89 without these symptoms.

On analysis of the data obtained, 75 % of Infertile women with galactorrhea and menstrual irregularities had hyperprolactinemia when compared to 8.30% in infertile women without galactorrhea and menstrual irregularities.

This association between the incidence of galactorrhea with menstrual irregularities in infertile women with and without hyperprolactinemic was statistically significant.

The Z value obtained was -1.94 lying within the range of -1.96 to +1.96. Level of freedom was (c-1) (r-1).

Figure - : Line Diagrammatic representation of Table-



VI. Relation With Hypothyroidism:

Table Showing Relation Between Hypothyroidism & Prolactin Levels

Hypothyroidism	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
Present	05 (5.62)	03 (27.2)	08
Absent	84 (94.38)	08 (72.3)	92
	89	11	100

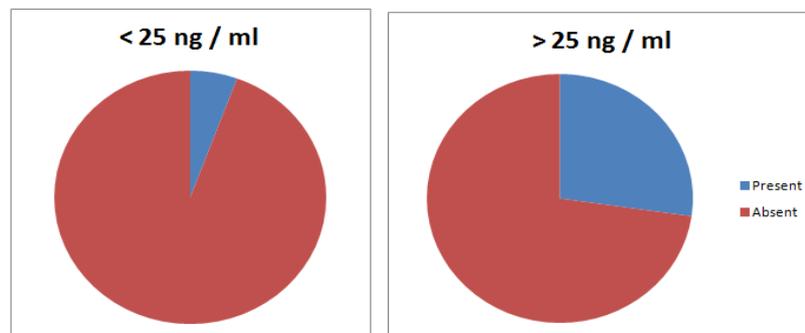
- 37.5% of Infertile women with Hypothyroidism were Hyperprolactinemic which is more than 9% in women without Hypothyroidism.

The 11 hyperprolactinemic women showed 27.2% incidence of hypothyroidism compared to 5.62% in 89 normoprolactinemic women.

Statistically the incidence of Hypothyroidism between infertile woman with and without Hyperprolactinemic was significant.

The Z value obtained was -1.58 lying within the range of -1.96 to +1.96.level of freedom was (c-1) (r-1).

Pie Diagrammatic representatin of Table



Vii. Comparing Incidence Of Various Symptomatology In Hyperprolactinemia

Menstrual problem,hypothyroidism and galactorrhoea had significantly higher Hyperprolactinemia as compared to other complaints.

other cases include normoprolactinemic and hypoprolactinemic cases.

In patients with serum prolactin more than 25 ng/ml, the main problem was in the menstrual cycle in 09 (81.81%) cases followed by galactorrhoea in 03 (27.27%), Hypothyroidism in 03 (27.27%) and pelvic pain in 01 (09.09%) cases. Only infertility, as the presenting complaint was found in majority; 37 (41.57%) cases with serum prolactin levels less than 25 ng/ml. It was observed that with increasing prolactin value, number of complaints too increased. Thus a statistically significant association between serum prolactin levels and number of complaints was found in the present study ($p < 0.001$)

Table Showing Mean Prolactin Values In Study Group

MEAN PROLACTIN LEVEL IN INFERTILE	VALUE (ng /ml)
Hyperprolactenemic women	74.74
Hypothyroid and Hyperprolactenemic women	112.7
Galactorrheac and Hyperprolactenemic women	115.62
With Menstrual Irregularities and Hyperprolactenemic women	76.6

As evident, by the above figures the mean prolactin levels in patients with alactorrhea and Hypothyroidism were higher (more than hundred) than those without.

ix. Significance Of Hyperprolactinemia In Infertile Women Compared To Fertile Woman (Parous, 20-30 Yrs, Not On Ocp, Non Lactating)

Table - Prolactin Levels In Fertile & Infertile Women

No. of Women	Prolactin Levels		Total
	≤ 25 ng/ml	> 25 ng/ml	
Infertile	89 (47.6)	11 (84.6)	100
Fertile	98 (52.4)	2 (15.3)	100
	187	13	200

There was an incidence of 11% hyperprolactinemia in Infertile women when compared to only 2 % in fertile women. These two fertile women with hyperprolactenemia were parous, lactated for more than 2 years, with only a slight elevation of prolactin -mean 28.5 ng/ml when compared to mean 74.74 ng/ml in infertile women with hyperprolactenemia.

To say it in other way 47.6% of normoprolactenemic women were infertile compared to 84.6% of 13 hyperprolactenemic women.

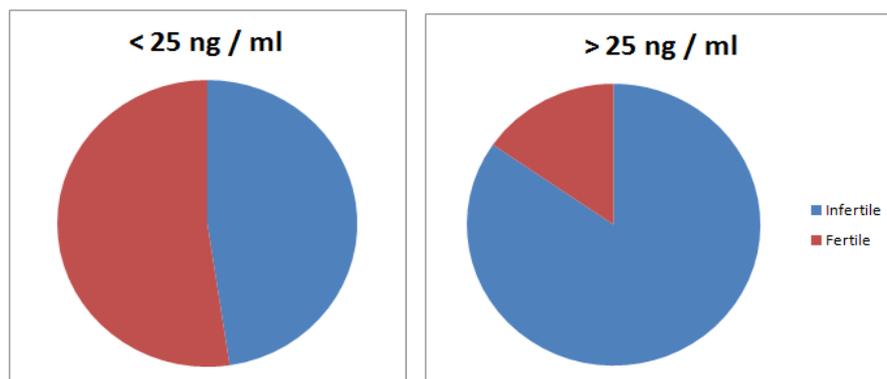
This difference in the incidence of hyperprolactinemia in infertile women and fertile women was found to be statistically significant.

Chi-square value after Yate's correction was 6.5 ($p < 0.05$). Anything more than 3.84 is significant (i.e $p < 0.05$)

All the secondary infertile women were having 1 live child, no history of abortions, /preterm births.

7 out of 11 hyperprolactenemic people conceived during the study period with cabergoline – 0.5mgs/wk given for an average of 2-3 cycles. In the other 4 cases follow up was lost.

Figure - XII: Pie Diagrammatic representation of Table -XII



V. Discussion

1) In the present study, out of 100 infertile women 62% are of primary infertility and 38% are of secondary infertility. In other studies it ranged from 60-70% and 30-40%.

2) Serum prolactin value was raised in 11% of the cases of infertile woman compared to 2% in the fertile woman. Thus a significant association ($p < 0.05$) between hyperprolactinemia and infertility was established in the present study. The incidence of hyperprolactinemia in the infertility group was reported ranging from 1.48% to 41.0% by various workers (Kredenster et al 1981, Pillai et al 1991, Pratibha et al 1993).

3) It was seen that amongst the hyperprolactinemic group, majority viz. 72.72% were of primary and 27.27% were of secondary infertility. Sinha et al (1989) reported the incidence of primary infertility in 65.81% and secondary infertility in 34.10% of the cases. (Table I)

The reason for hyperprolactinemia in parous women leading to secondary infertility was due to oestrogen of pregnancy which is enough to stimulate the growth of a small silent tumor of pituitary leading to amenorrhoea, persistent galactorrhoea and secondary infertility (Sherman et al, 1978). It is believed that the main cause of infertility associated with hyperprolactinemia is anovulation due to the impairment in the gonadotrophin release pulsatility, interference in the positive feedback of oestrogen on the mid cycle LH surge and direct inhibition of ovarian steroidogenesis (Salvi 1998).

4) On analyzing the presenting complaint along with infertility in hyperprolactinemic women, it was seen that the maximum cases had menstrual problems (81.8%) followed by galactorrhoea in 28% of infertile group (Table VII & VI). The presence of multiple complaints in the infertile hyperprolactinemic cases was significantly more ($p < 0.001$) than in normoprolactinemic infertile cases. According to Franks et al (1977), the characteristic reproductive disturbances associated with hyperprolactinemia include primary or secondary amenorrhoea, symptoms and signs of oestrogen deficiency (vasomotor symptoms, decreased breast size, vaginal dryness, vaginal atrophy and osteoporosis). Various workers state that hyperprolactinemia may present with galactorrhoea, menstrual disturbances, infertility or they may be asymptomatic (Conner and Fried, 1998 and Salvi, 1998). The present study is in complete agreement with the above workers.

5) Galactorrhoea, which is one of the commonest complaint reported by hyperprolactinemic cases in the present series, was present in 28% of the hyperprolactinemic cases (Table VII). Similar findings have also been reported by various authors (Takkar et al 1986, Sinha et al 1989, Rajan 1990, Pillai et al 1991 and Sheth & Sheth, 1992).

Hyperprolactinemia is not always associated with galactorrhoea. Out of 100 study cases, 95 (95%) cases and out of 11 hyperprolactinemic cases, 8 (72.7%) cases did not have galactorrhoea (Table V). Katz and Adashi (1990) commented that absence of galactorrhoea in hyperprolactinemic cases may be due to the presence of an immunoreactive and therefore measurable prolactin referred to as "big" prolactin and "big - big" prolactin which may lack bioactivity. In view of the fact that the hyperprolactinemic cases had highly significant association with galactorrhoea ($p < 0.001$) in our study, we believe that galactorrhoea is a typical marker of hyperprolactinemia.

6) An attempt was made to correlate the association of menstrual irregularities and galactorrhoea with hyperprolactinemia. In our study 75% cases having both menstrual irregularities and galactorrhoea had hyperprolactinemia. (Table VIII)

Quigley & Haney (1980) reported, that of the cases with menstrual irregularities and galactorrhoea, between 79% 97% have hyperprolactinemia. Also according to Kredentser et al (1981), when infertility was combined with abnormal menstruation or galactorrhoea or both, the incidence of hyperprolactinemia increased. The present study also showed close association of menstrual irregularities and galactorrhoea in infertile women with hyperprolactinemia.

Amongst the various menstrual abnormalities in hyperprolactinemic cases, oligohypomenorrhoea was commonest & present in 41% case, followed by oligomenorrhoea in 41% cases and secondary amenorrhoea in 23% of the cases. Rajan (1990) found the incidence of secondary amenorrhoea and oligomenorrhoea in hyperprolactinemic cases to be 23% and 16% respectively. Katz and Adashi (1990) attribute oligomenorrhoea and amenorrhoea in hyperprolactinemic cases to a compensatory increase in hypothalamic dopamine in response to hyperprolactinemia, ..

7) The incidence of hypothyroidism in hyperprolactinemia was 27% i.e. 3 out of 8. (Table IX)

The mean serum prolactin level in hypothyroid women was 112.6 ng/mL. The incidence of hypothyroidism in hyperprolactinemia was statistically highly significant. The ratio of proportions between hyperprolactinemia and hypothyroidism was nearly 4: 1 i.e. in every four hyperprolactinemic patients one had

hypothyroidism. The most common cause of hyperprolactinemia in our study was idiopathic followed by primary hypothyroidism.

8) Obesity & Hyperprolactinemia

Increased body weight was found to be associated with hyperprolactinemia in various studies. 63.6% of hyperprolactinemic patients were found to be having BMI more than 25. Greenman Y, Toidjman k, Stem N found a correlation between hyperprolactinemia and BMI. There was also increased incidence of insulin resistance in these cases.

VI. Conclusions

Prolactin Level estimation in 100 cases of female infertility and its relation with various symptomsatology is presented in my study for a period of 14 months. Conclusions reached are

1. Primary infertility was found in 62% of the cases and secondary infertility in 38% of the cases.
2. The mean age group of primary infertility was 24 years and that of secondary infertility 28 years.
3. Incidence of Hyperprolactinemia was 11% in infertile women when compared to 2% in fertile women.
4. The correlation between obesity and hyperprolactinemia was statistically significant, 6.7% of obese women were hyperprolactinemic compared to 6.9% of Non obese women.
5. Serum prolactin levels were elevated to a statistically significant level in infertile women with galactorrhea, menstrual irregularities and hypothyroidism.
6. Moreover the Serum prolactin levels were more significantly elevated in patients with both galactorrhea and menstrual irregularities.
7. The mean serum prolactin levels were higher in infertile woman with hypothyroidism or galactorrhea than in infertile women without hypothyroidism or galactorrhea.

Since the incidence of hyperprolactinemia is very high in women with galactorrhea and quite high in women with oligomenorrhea/anovulation, a search for galactorrhea and measurement of serum prolactin levels are important screening procedures in all women who are not ovulating normally. The relatively high occurrence of abnormal TSH levels in women with ovulatory dysfunction and oligomenorrhea emphasizes the importance of TSH screening in these women. Therefore Serum prolactin levels are mandatory in all infertile women.

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