



Hyperprolactinemia and its correlation with hypothyroidism in infertile women

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OBJECTIVE(S) : To find out the incidence of hyperprolactinemia in female infertility after excluding tubal factor and male factor, and to find its correlation with hypothyroidism.

MATERIAL(S) : One hundred and eleven women attending the out patient department of Obstetrics and Gynecology were included in the study. The exclusion criteria were male factor infertility, and amongst the female factors tubal factor, congenital anomaly of the urogenital tract and any obvious organic lesion.

RESULT(S) : Sixty percent women had primary infertility and 40% had secondary infertility. Anovulatory/oligo-ovulatory cycles were detected in 49.5% (49% and 50% in primary and secondary infertility respectively). Galactorrhea was present in 9% of the women. The incidence of hyperprolactinemia i.e. serum prolactin levels > 25 ng/mL was 46%. The mean serum prolactin level in hyperprolactinemic women was 76.53 ± 55.97 ng/mL (range 48.3 to 200 ng/mL). The incidence of hypothyroidism in hyperprolactinemia was 25.5%.

CONCLUSION : There is a high incidence of hyperprolactinemia in infertile women. A positive correlation of 1:4 was found between hypothyroidism and hyperprolactinemia.

Key words : hyperprolactinemia, infertility, hypothyroidism, galactorrhea

Introduction

Hyperprolactinemia is usually associated with menstrual and ovulatory disorders like amenorrhea, oligomenorrhea, anovulation, ovulatory cycles with short or inadequate luteal phase, and galactorrhea¹. Approximately two thirds of women having both galactorrhea and amenorrhea will have hyperprolactinemia. Of that group, approximately one third will have a pituitary adenoma². 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 been 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 (T_4) 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 prolactin³. The aims of the study were to find the incidence of hyperprolactinemia in female infertility after exclusion of tubal factor and male factor infertility, and to study its correlation with hypothyroidism.

Methods

The study was conducted on 111 infertile women. The exclusion criteria were male factor infertility and amongst the female factors tubal factor, any congenital anomaly of the urogenital tract, and any obvious organic lesion. A detailed history was taken, examination carried out and the infertility

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workup done which included semen analysis, premenstrual endometrial sampling, hysterosalpingography, ultrasonography, serum prolactin levels, diagnostic laparoscopy when indicated, and serum TSH levels in cases of hyperprolactinemia. 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 2-8°C 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 from Boehringer Co. Women with serum prolactin levels > 100 ng/mL were advised CT scan or MRI.

Results

Of the 111 patients, 67 (60%) had primary infertility and 44 (40%) secondary infertility. Most of the women were in the age group of 24-28 years in both the groups. The mean duration of infertility in the patients with primary infertility was 4.58 years and in those with secondary infertility 3.39 years. Galactorrhea was present in 10 (9%) of the total infertile patients, in five (5/67; 8%) with primary infertility and in five (5/44; 11%) with secondary infertility. Galactorrhea was either the chief complaint or was detected on clinical examination. Normal menstrual cycles were present in 47 (42%; 47/111) infertile patients, 31 (46%; 31/67) with primary infertility and 16 (36%; 16/44) with secondary infertility. The remaining 64 showed some menstrual abnormality as shown in Table 1. Premenstrual endometrial sampling was done in all 111 infertile patients and 55 (49.5%; 55/111) showed nonsecretory endometrium suggestive of anovulatory / oligo-ovulatory cycles. Of these, 33 (49%; 33/67) had primary infertility and 22 (50%; 22/44) secondary infertility. Tuberculosis was detected in six (5.4%; 6/111) patients, four (6%; 4/67) with primary infertility and two (4.5%; 2/44) with secondary infertility. The remaining 50 (46.1%; 50/111) women showed

Table 1. Menstrual disturbance and hyperprolactinemia (n=111).

Clinical condition	(n=111)		Normal prolactin levels		Hyperprolactinemia	
	Number	Percentage	(n=60)	Percentage	(n=51)	Percentage
Regular menses	47	42	28	47	19	37
Oligomenorrhea / Hypomenorrhea	56	50	29	48	27	53
Amenorrhea	6	6	3	5	3	6
Menorrhagia	2	2	0	—	2	4
Total	111	100	60	100	51	100

secretory endometrium. On hysterosalpingography, all the patients had patent fallopian tubes as none with tubal factor infertility was included in the study. Ultrasonography was done in all the patients and showed no abnormality in 60 (90%; 60/67) women with primary infertility and 39 (89%; 39/44) women with secondary infertility. Fibromyomas were found in two women with secondary infertility and in none with primary infertility. Table 2 shows the various pathologies found on USG in the two groups. Diagnostic laparoscopy was done in 25 patients: 15 with primary and 10 with secondary infertility (Table 3). Table 4 shows the serum prolactin levels. The incidence of hyperprolactinemia (>25 mg/mL) was 46% (51/111) overall, and 49% (33/67) and 40% (18/44) in the primary and secondary infertility groups respectively. The mean

serum prolactin level in hyperprolactinemic women was 76.53 ng/mL. Anovulation was detected in 30% (18/60) of the women with normoprolactinemia and 73% (37/51) with hyperprolactinemia. Thirteen women had prolactin levels > 100 ng/mL; nine (14%; 39/67) with primary infertility and four (9%; 4/44) with secondary infertility. All the 13 were advised CT scan or MRI but only six could afford it. One woman in each group had pituitary adenoma and both had serum prolactin levels > 200 ng/mL. The remaining four showed normal findings. X-ray of the skull was normal in the other seven women who could not afford CT scan or MRI. Table 5 shows the serum TSH levels in 51 hyperprolactinemic women. The incidence of hypothyroidism in hyperprolactinemia was 25.5% i.e. 13 out of 51. Of these, nine (27%; 9/33) women had primary infertility and four

(22%;4/18) secondary infertility. The mean serum prolactin level in hypothyroid women was 124.4 ± 64.32 ng/mL. The mean serum TSH level in women with hyperprolactinemia was 9.57 ± 16.74 (range 1.05–86.21) μ IU/mL and in hypothyroid women with hyperprolactinemia 27.88 ± 32.57 (range 5.6-86.3) μ IU/mL. This difference was statistically highly significant ($p=0.0004$). The ratio of proportions between hyperprolactinemia and hypothyroidism was 4:1 i.e.

in every four hyperprolactinemic patients one had hypothyroidism. Thus there was a positive correlation. Out of the 10 patients with galactorrhea, nine (90%) had hyperprolactinemia. The mean serum prolactin levels in women with galactorrhea was 127.1 ng/mL. Out of the 51 women with hyperprolactinemia, nine (18%) had galactorrhea. The most common cause of hyperprolactinemia in our study was idiopathic (59%;20/51) followed by primary hypothyroidism (19.6%;10/51).

Table 2. Abnormal findings on ultrasonography.

Findings	Primary infertility (n=67)	Secondary infertility (n=44)
Uterine pathology		
Endometrial hyperplasia	1	0
Fibroids	0	2
Tubal pathology	0	0
Ovarian pathology		
Polycystic ovaries	4	2
Adnexal cyst	2	0
Chocolate cyst	0	1

Table 3. Findings on diagnostic laparoscopy (n=25).

Findings	Primary infertility (n=15)	Secondary infertility (n=10)
No abnormality	4	1
Polycystic ovaries	4	2
Endometriosis	3	5
Fimbrial cyst	2	1
Bulky uterus	1	0
Flimsy adhesious	1	1
Abnormal findings	15	10

Table 4. Serum prolactin levels (n=111).

Serum prolactin level (ng/mL)	Primary infertility (n=67)	Percentage	Secondary infertility (n=44)	Percentage	P value
0 – 25	34	51	26	60	0.147
26 – 100	17	25	6	14	0.109
51 – 100	7	10	8	18	0.129
101 – 150	3	5	2	4	0.316
151 – 200	1	2	1	2	0.181
>200	5	7	1	2	0.128
Total	67	100	44	100	

Table 5. Serum TSH levels in hyperprolactinemia (n=51).

Serum TSH level (mIU/mL)	Primary infertility (n=33)	Percentage	Secondary infertility (n=18)	Percentage
< 5	24	73	14	78
5 - 10	3	9	1	5.5
10 - 20	1	3	1	5.5
> 20	5	15	2	11
Total	33	100	18	100

Discussion

Hyperprolactinemia is a common problem encountered in reproductive disorders⁴. 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. In our study, there were 60% women with primary infertility and 40% with secondary infertility. The menstrual pattern was abnormal in majority of infertile women in both the groups (54% with primary infertility and 64% with secondary infertility). Such findings have been reported by other authors also^{1,4}.

Galactorrhea was present in 9% of the total women (8% with primary infertility and 11% with secondary infertility). The incidence of galactorrhea in hyperprolactinemic women was 18%. A 25% incidence has been reported¹. The incidence of hyperprolactinemia in women with galactorrhea was 90% in our study. An incidence of 62.16% has been reported⁵. On premenstrual endometrial sampling, 49% women with primary infertility and 50% with secondary infertility showed non-secretory endometrium (49.5% of all infertile women), and hence anovulatory cycles. Among the causes of infertility in women, ovulatory dysfunction has been reported in 31.4%⁵ and in 51.4%¹.

In our study, sonography was done in all 111 women and positive findings were seen in 12 only. However, diagnostic laparoscopy was done in 25 women and positive findings were seen in 20 (80%) of them. The difference of proportions test shows a Z value of 7.216 for diagnostic laparoscopy as compared to sonography. Thus the former is a better tool for diagnosing pelvic pathology in cases of infertility.

The incidence of hyperprolactinemia in our study is 46%. Mishra et al¹ have reported an incidence of 20% in infertility with menstrual irregularities. Our incidence of hyperprolactinemia is more, probably because the cases of tubal factor infertility were excluded. The mean prolactin level in hyperprolactinemic women in our study is 76.33 ± 55.97 ng/mL whereas Mishra et al¹ found it to be $128.28 \pm$

12.74 ng/mL. Our incidence of hypothyroidism in hyperprolactinemic women is 25.50% (13/51). So, a positive correlation of 1:4 was found between hypothyroidism and hyperprolactinemia. Choudhary and Goswami⁴ observed hyperprolactinemia in 16.6% and Singh et al⁶ in 57% of women with hypothyroidism.

It would be interesting to find out the incidence of hypothyroidism in infertile women with normal prolactin levels and compare it with the incidence in hyperprolactinemic infertile women.

Conclusion

Serum prolactin levels are mandatory in all infertile women especially those with oligomenorrhea and amenorrhea. 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.

References

1. Mishra R, Baveja R, Gupta V et al. Prolactin level in infertility with menstrual irregularities. *J Obstet Gynecol India* 2002;52:40-3.
2. Hershlag A, Peterson CM. Endocrine disorders. In: *Novak's Gynecology*. 12th edn. Maryland, USA, Williams and Wilkins 1996;833-86.
3. Shoupe D, Mishell DR. Hypoprolactinemia: Diagnosis and treatment. In: *Mishell's textbook of Infertility, Contraception and Reproductive Endocrinology*. 4th edn. Massachusetts. Blackwell Science. 1997: 323-41.
4. Choudhary SD, Goswami A. Hyperprolactinemia and reproductive disorders-a profile from north east. *J Assoc Physicians India* 1995;43:617-8.
5. Rajan R. Prolactin metabolism in infertility. *J Obstet Gynecol India* 1990;40:243-7.
6. Singh L, Agarwal CG, Chowdhary SR et al. Thyroid profile in infertile women. *J Obstet Gynecol India* 1990;40:248-53.