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PROLACTIN AND THYROID HORMONE STATUS IN INFERTILE WOMEN

Gyanecology

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ABSTRACT

The overall incidence of infertility has remained relatively unchanged over the past 3 decades however the evaluation and treatment of infertility have changed dramatically since that time. Infertility is a medical problem that affects a vast proportion of the world's young population (10-15%). In present study around 250 cases are taken and after excluded abnormal male factor, fallopian tube, any organic pathology and other exclusion criteria discuss above 100 cases were taken and study was conducted.

Both hypothyroidism and hyperprolactinemia may result in menstrual disorders. Oligomenorrhoea was most common in infertile women. Hypothyroidism is commonly associated with hyperprolactinemia and such patients exhibit ovulatory failure. Hence, assessment of serum TSH and prolactin levels are mandatory in the work up of all infertile women, especially those presenting with menstrual irregularities.

The treatment of hyperprolactinemia with dopamine agonist can normalize circulating prolactin levels. Bromocriptine is administered in 2 to 3 divided doses with a total of 2.5-40 mg/dl. The dose is slowly advanced every 4 to 10 days as tolerated until the serum prolactin is normalized and the symptoms are relieved. Cabergolin administered at 0.25-2 mg once or twice weekly is much potent and better tolerated than bromocriptin.

Being infertile is a stress to the individual, family and to the society as whole. Proper diagnosis and treatment of causative factors in this condition can help them to conceive early and lead to a better social life.

KEYWORDS

Infertility, Young Population, Hypothyroidism And Hyperprolactinemia

INTRODUCTION

Infertility is a medical problem that affects a vast proportion of the world's young population (10-15%). The inability to bear children impacts the psychological and emotional lives of the couples who face this condition[1]

Hormonal disorders of female reproductive system are comprised of a number of problems resulting from aberrant dysfunction of hypothalamic-pituitary-ovarian axis. Clinical and experimental studies have suggested a close relationship between the hypothalamic-pituitary- thyroid axis and the hypothalamic-pituitary-ovarian axis[2]. Proper evaluation of hormonal disorders involves a multidimensional diagnostic approach, with a pivotal contribution from clinical laboratories[3].

Measurement of thyroid hormones and prolactin has been considered an important component of infertility workup in women[4]. Thyroid dysfunctions interfere with numerous aspects of reproduction and pregnancy. Several articles have highlighted the association of hypothyroidism or hyperthyroidism with menstrual disturbance, anovulatory cycles, decreased fecundity and increased morbidity during pregnancy[5,6,7].

The prevalence of hypothyroidism in women in the reproductive age (15-45 years) varies between 2% and 4% [8, 9]. Despite normal thyroid stimulating hormone (TSH) and free thyroxin (FT4) concentrations, some patients may exhibit the clinical picture of hypothyroidism. In response to hypothyroid state a compensatory increase in the discharge of central hypothalamic thyrotropin releasing hormone occurs, which results in stimulation of prolactin (PRL) production, leading to hyperprolactinemia. Hyperprolatinemia adversely affects the fertility potential by impairing pulsatile secretion of gonadotropin releasing hormone (GnRH) and hence interfering with ovulation [5,10]. The prevalence of hyperthyroidism in infertility is about 8% in the study by Goswami et al[11] and 3.07% by Sharma et al[12]. The precise impact of hyperthyroidism on fertility is still ill-defined.

Awareness of thyroid and prolactin states in the infertile couple is crucial because of its significant, frequent and often reversible or preventable effect on infertility. The present study age matched primary infertile females were compared with normal fertile females to assess status of prolactin and thyroid stimulating hormone (TSH). Approximately 85-90% of healthy young couples conceive within 1 year, most within 6months[13,14,15]. Infertility therefore affects approximately 10-15% of couples and is an important part of practice of many clinicians.

Infertility can be primary or secondary. In primary infertility, couples have never been able to conceive, while in secondary infertility, in which a prior pregnancy, although not necessarily a live birth has occured.

Definition of infertility differ with demographers tending to define infertility as childlessness in a population of women of reproductive age while the epidemiological definition is based on Trying for' or Time to' a pregnancy, generally in a population of women exposed to a probability of conception.[16,17]

Infertility is a worldwide problem affecting people of all communities, though the cause and magnitude may vary with geographical location and socioeconomic status, approximately 8-10% couples within the reproductive age group present for medical assessment, generally following 2 years of failed effort to reproduce.

Data explored from WHO by the ICMR suggest that approximately 13-19 million couples are likely to be infertile in India at any given time. (ICMR & NAMS 2005)[18]

In any series of infertile marriages, the main etiological factor is found in the females in about 40% of cases; about 35% of the husbands concerned have some degree of infertility. In 10-20% of cases, a combination of factors operates and the rest have unexplained infertility.

Aims & objectives of our study

1. To detect the prevalence of hypothyroidism in subfertile women.
2. To identify prevalence of hyperprolactinaemia in subfertile women.

3. To evaluate the combined effect of hypothyroidism & hyperprolactinaemia in those cases.

MATERIALS AND METHODS

The Observational Study diagnosed 100 cases of primary infertile females attending the outpatient department of obstetrics and gynecology, I. P. G. M. E&R, S. S. K. M Hospital,Kolkata are included & were followed till conception from Jan. 2017 - June 2018

INCLUSION CRITERIA

1. Clinically diagnosed cases of primary infertile women.
2. Age between 15-45years.
3. Duration of marriage more than one year.
4. The patient understood and signed the study specific informed consent and agreed to comply with the study.

EXCLUSION CRITERIA

1. Abnormal Male factors of infertility.
2. Abnormal Tubal factors of infertility.
3. Any congenital anomaly of uro-genital tract.
4. Any obvious organic lesion.
5. Patients who have undergone previous thyroid surgery or on thyroid medications.
6. Husband not having any physical relationhip with his wife.
7. Patient diagnosed to have any gynaecological pathology detected by USG like uterine, tubal, adenexal pathology.
8. Patient diagnosed as a case of PCOS.
9. Patient diagnosed as a case of hyperinsulinemia.

In the period of study 250 cases of primary infertility was taken and 150 cases were excluded under above exclusion criteria with any pathological condition diagnosed by USG and laboratory investigation and 100 cases were taken for study.

METHODS:

History & routine clinical examination and other relevant investigations i.e. abdominal and pelvic examination, routine blood investigation, trans-abdominal USG, Thyroid profile (FT3, FT4, TSH) and serum prolactin.

PLAN FOR DATA ANALYSES:

All data collected and entered into an EXCEL spread sheet and was analysed to derive significance and correlation by using SPSS (statistical, package for social science) and appropriate statistical tools.

RESULT & ANALYSIS

We found that 25(25.0%) patients had ≤25Yrs age group, 35(35.0%) patients had 26-30 Yrs age group, 36(36.0%) patients had 31-35 Yrs age group and 4(4.0%) patients had 36-40 Yrs age group.We found that the mean of age (mean±s.d.) of the patients was 28.8900 ± 4.0995 years with range 21.0000- 37.0000.

It was showed that 8(8.0%) patients had duration of infertility 2 years, 21(21.0%) patients had duration of infertility 3 years, 15(15.0%) patients had duration of infertility 4 years, 22(22.0%) patients had duration of infertility 5 years, 16(16.0%) patients had duration of infertility 6 years, 8(8.0%) patients had duration of infertility 7 years, 4(4.0%) patients had duration of infertility 8 years, 5(5.0%) patients had duration of infertility 9 years and 1(1.0%) patients had duration of infertility 10 years.

We found that as per WHO, Lower literacy group (early home education - lower secondary upto 7th class), Middle literacy group (upper secondary- post secondary non tertiary upto +2), Higher literacy group (short cycle tertiary - doctorate level), In my study 40(40.0%) patients had higher education, 22(22.0%) patients had lower education and 38(38.0%) patients had medium education.

We found that 19(19.0%) patients had higher SE status, 23(23.0%) patients had lower SE status and 58(58.0%) patients had medium SE status according to modified Kuppuswamy Scale. Our study found that 16(16.0%) patients had abnormal M/H, 4(4.0%) patients had dysmennorhea M/H, 8(8.0%) patients had menorrhagia M/H, 12(12.0%) patients had metromenorrhagia M/H, 25(25.0%) patients had normal M/H, 28(28.0%) patients had oligomenorrhoea M/H, 1(1.0%) patients had oligomenorrhoea + dysmennorhea M/H and 6(6.0%) patients had polymenorrhoea M/H.

It showed that 8(8.0%) patients had Diabetes Melitus. We found that per abdomen finding in all cases normal. It was showed that per speculam finding in all cases within normal limit. We found that 5(5.0%) patients had abnormal Per Vaginal and 95(95.0%) patients had normal P/V findings.

Our study found that the mean of TSH (mean±s.d.) of the patients was 8.8253± 8.5269 mIU/L with range 0.1100- 36.2400 mIU/L and the median was 5.2100 mIU/L.We found that 43(43.0%) patients had euthyroid status of TSH, 53(53.0%) patients had hypothyroidism status of TSH and 4(4.0%) patients had hyperthyroidism status of TSH.It was showed that the mean of FT3 (mean±s.d.) of the patients was 2.5658 ± .8025 with range 1.2600-6.1200 and the median was 2.4500.

We found that the mean of FT4 (mean±s.d.) of the patients was 1.7068 ± .5762 with range 0.6600- 4.2200and the median was 1.6700.Our study found that 36(36.0%) patients had hyperprolactinemia and 64(64.0%) patients had normal prolactin status.It was showed that the mean of prolactin (mean±s.d.) of the patients was 23.9750 ± 15.7091with range 0.6600- 99.8000 and the median was 20.1500.

We found that all patients had normal adenexal finding. It was showed that all patients had normal tubes and normal Uterus as per HSG examination. Our study found that all patients had normal Uterus as per USG. It was showed that 22(22.0%) patients did NOT conceive, 18(18.0%) patients did not take medicine/follow up and 60(60.0%) patients had conceived after treatment. We found that association between TSH status vs. prolactin status was statistically significant ($p<0.0001$).

We found that kappa value is 44.2%. So it is intermediate to good agreement between thyroid & prolactin in case of infertile women.

DISCUSSION

In my present study 35% cases having primary infertility comes in the age group of 26-30 years, 25% patients under the age range 21-25, and 40% present after the age 30.

The study of Maheswari et al[19] showed that fertility is at its peak between the ages of 18 and 24 yrs, while it begins to decline after age 27 and drops at a somewhat greater rate after age 35. So my study is similar to this result.

Another study of Taylor et al [20] described that fertility begins to decline in females from the age of 30, although the reduction in fertility is greatest in women in their late 30s and early 40s. For women up to 25 years old the cumulative conception rate is 60% at six months and 85% at one year, but conception rates for women aged over 35 are less than half of this.

As studied by Roupa Z et al 21 which consisted of 110 infertile women, regarding age, 64.5% were 20-29 years old, 20.0% were 30-39 years old, 11.8% were 40-49 years old and 3.7% were over 50 years old. The present study is almost similar to both the previous studies. Table 3- shows the duration of infertility for most of the cases were 5 years interval i.e 22% cases, a period of 3 years found in 21% of cases, and 1% of patients present with a duration of infertility of 10 years duration. As per Roupa Z et al study regarding period of infertility 3 years is found be 21% and 4 to 5 years was 20%.So present study is nearly similar to this study.

WHO has classified the socio-economic status as per capita annual income into low, middle and high income group. Present study on socio economic distribution shows 24.5% cases belong to low socio economic status, 53% cases belong to middle socio economic status and 22.5% of cases belong to high socio economic status. My present study shows 24% belong to low literacy group, 31% high literacy and 45% patients come from middle literacy group.

As per Roupa Z et al [21] It was seen that maximum number of infertile patients belongs to middle socio-economic status and middle literacy group. My study is comparable to above study. The cause may be that tertiary health services are not easily approachable to low socioeconomic and low literarcy group people or they may be ignorant that infertility is a health problem. The low proportion of High socio economic group in our study may be due to their opting for private sector care.

In the present study the most common menstrual disorder that patient complained was Oligomenorrhoea constituting 28% reflecting ovulatory disorder being the most common cause, menorrhagia and

metromenorrhagia constituting of 8% &12% respectively. Amenorrhoea found to be 8%. 25% patients had normal menstrual flow and least common disorder is Dysmenorrhoea.

The study carried by Goswami et al 22 shows a menstrual disorders (mainly oligomenorrhea), were reported by about 60% of the infertile women. Fifty percent of the subjects with hypothyroidism had menstrual irregularities, presented with amenorrhea. My study shows less oligomenorrhic patient than above study as cases having PCOS and any gynaecological pathology was excluded. But according to Krasses et al,23 the prevalence of menstrual irregularities (mainly oligomenorrhea) reached 23% among hypothyroid patients and present study shows similar results.

Present study shows 53% of total infertile patients belong to hypothyroidism, whereas 4% from hyperthyroidism, and 43% belong to euthyroid. The prevalence of hypothyroidism in women of reproductive age (20-40 years) varies in the study of Goswami et al22 between 2% to 4%. Most infertile women (87%) were euthyroid and 5% cases are hyperthyroidism. But in present study it was found be high prevalence of hypothyroidism.

Most of the infertile women (77.5%) were euthyroid in the study of Santosh Fupare et al24 and the prevalence of hyperthyroidism in the cases were (4%). Hypothyroidism was seen in (18%) of the infertile women. Study of Flooja Nupur et al 25showed among infertile women, 52.5% of cases were euthyroid, 30% hypothyroid and 17.5% was hyperthyroid. But it was came to be (36%) hypothyroidism in Sharma et al study.So my study it is not comparable.

Study on (Table) shows 36% of total infertile patients belong to hyperprolactinemia, and 64% having normal prolactin value. In Goswami et al 22 study hyperprolactinemia was depicted in 41% of the infertile women and the incidence of hyperprolactinemia was 46% among primary infertility cases according to the study by Avasthi Kumkum et al 26. So my present study showing similar result to both studies.

The study of Omer Mohamed Shoaib et al27 shows hyperprolactinemia is more commonly seen in patients suffering from primary infertility which was found to be (76%) as compared to Hooja Nupur25 et al study which was 28%. But Sharma et al 28 gave higher occurrence of hyperprolactinemia (59.37%) in infertile women.

Study of Santosh Fupare et al 2 found a rise in serum FT4 and FT3 in the infertile group which was non-significant and similarly in studies of Kumkum et al, Hooja Nupur et al it was found to be non-significant.

Present study shows that out of 36 hyperprolactinemic infertile women 32 are hypothyroid therefore incidence of hypothyroidism in hyperprolactinemic infertile women is 88.9% and was statistically significant (p valu <0.01).

As per Santosh Fupare et al 24 Prolactin and TSH were positively correlated with each other. Therefore, we can say that hyperprolactinemia & hypothyroidism plays key role in etiopathogenesis of infertility. As per the study, they observed a greater percentage of infertile women with hypothyroidism exhibiting hyperprolactinemia (40.7%). The findings in this study strongly correlate with the findings of study by Goswami Binita et al22, they found 46.1% infertile women with hypothyroidism had hyperprolactinemia. Present study showing similar result to above study.Flooja Nupur et al 25 there was significant correlation between serum TSH and Prolactin levels and infertility.80% women with raised prolactin and abnormal thyoid levels were infertile.

Study shows Out of 100 cases 15 cases(15%) conceive after 18-24 months of treatment and 47(47%) cases after 8-18 months and 38(38%) of cases were lost to follow up regarding conception. As per Indu Verma et al 29 study 23.9% were hypothyroid after treatment for hypothyroidism, 76.6% of infertile women conceived within lyr to 1.34 year. Infertile women with both hypothyroidism and hyperprolactinemia also responded to treatment and their PRL levels returned to normal. So similar result was also obtained by my study.

Study shows Out of 100 cases only 60% cases conceived after treatment and 18% cases had not taken medication properly and 22% cases did not conceive after medication. Study of Indu Verma et al 29 showed after treatment of hypothyroidism and hyperprolactinemia the conceive rate was 58%.Present study shows similar result.

One study shows Out of 100 cases 40 cases conceived after treatment of hypothyroid and hyperprolactinemia. Treating hypothyroid and hyperprolactinemia significantly increases the rate of conception.

CONCLUSION

From the present study it can be concluded that:

- Most of Infertility cases, (40%) cases belonged to the age group of above 30 years.
- Mean duration of infertility in most of the cases was 5 years(22%)
- The most common menstrual disorder encountered was Oligomenorrhoea constituting 28% reflecting ovulatory disorder.
- Most of cases 53% of total infertile patients suffer from hypothyroidism, whereas 4% from hyperthyroidism.
- Hyperprolactinemia was noted in 36% of infertile women.
- Out of 36 Hyperprolactinemic infertile women 32 are Hypothyroid therefore incidence of hypothyroidism in hyperprolactinemic infertile women is 88.9%.
- Correlation between TSH level and prolactin level was statistically significant.

Table: Distribution Of Age, Duration Of Infertility, Education, Socio Economic Status, Menstrual History, Previous Illness, Per Abdomen, Per Speculam And Per Vaginal

		Frequency	Percent
Age (Yrs)	≤25Yrs	25	25.0%
	26-30Yrs	35	35.0%
	31-35Yrs	36	36.0%
	36-40Yrs	4	4.0%
	Total	100	100.0%
Duration of Infertility (Years)	2	8	8.0%
	3	21	21.0%
	4	15	15.0%
	5	22	22.0%
	6	16	16.0%
	7	8	8.0%
	8	4	4.0%
	9	5	5.0%
	10	1	1.0%
	Total	100	100.0%
Education	Higher	40	40.0%
	Lower	22	22.0%
	Medium	38	38.0%
	Total	100	100.0%
Socio- Economic Status	Higher	19	19.0%
	Lower	23	23.0%
	Medium	58	58.0%
	Total	100	100.0%
Menstrual History	Abnormal	16	16.0%
	Dysmennorhea	4	4.0%
	Menorrhagia	8	8.0%
	Metromenorrhagia	12	12.0%
	Normal	25	25.0%
	Oligomenorrhoea	28	28.0%
	Oligomenorrhoea + Dysmennorhea	1	1.0%
	Polymenorrhoea	6	6.0%
	Total	100	100.0%
Previous Illness	Diabetes Melitus	8	8.0%
	NO	92	92.0%
	Total	100	100.0%
Per Abdomen	Normal	100	100.0%
	Total	100	100.0%
Per Speculam	Normal	100	100.0%
	Total	100	100.0%
Per Vaginal	Abnormal	5	5.0%
	Normal	95	95.0%
	Total	100	100.0%

Table: Distribution Of Mean Age, TSH, FT3, FT4 And Prolactin

	Number	Mean	SD	Minimum	Maximum	Median
Age (Yrs)	100	28.8900	4.0995	21.0000	37.0000	
TSH	100	8.8253	8.5269	0.1100	36.2400	5.2100
FT3	100	2.5658	.8025	1.2600	6.1200	2.4500

Ft4	100	1.7068	.5762	0.6600	4.2200	1.6700
Prolactin	100	23.9750	15.7091	4.3000	99.8000	20.1500

Table: Distribution of TSH status, prolactin status, Adenexa USG, TUBES HSG, Uterus HSG and Conceive

		Frequency	Percent
TSH STATUS	EUTHYROID	43	43.0%
	HYPERTHYROIDISM	4	4.0%
	HYPOTHYROIDISM	53	53.0%
	Total	100	100.0%
Prolactin Status	HYPERPROLACTINEMIA	36	36.0%
	NORMAL PROLACTIN	64	64.0%
	Total	100	100.0%
Adenexa USG	Normal	100	100.0%
	Total	100	100.0%
TUBES HSG	NORMAL	100	100.0%
	Total	100	100.0%
Uterus HSG	NORMAL	100	100.0%
	Total	100	100.0%
Conceive	Not CONCEIVE AFTER TREATMENT	22	22.0%
	Not KNOWN	18	18.0%
	Conceive After Treatment	60	60.0%
	Total	100	100.0%

Table: Showing Relation Between Thyroid Vs. Prolactin In Case Of Infertile Women.

THYROID	PROLACTIN		TOTAL	p-value
	NORMAL	ABNORMAL		
NORMAL	39	4	43	0.442 (95% confidence interval 0.263 – 0.621)
ABNORMAL	25	32	57	
TOTAL	64	36	100	
EUTHYROID	39	4	43	Chi-square value: 29.2224, p-value: <0.0001
HYPERTHYROIDISM	4	0	4	
HYPOTHYROIDISM	21	32	53	

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