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"STUDY THE CORRELATION OF HYPERPROLACTINEMIA, THYROID DISORDERS AND MENSTRUAL PATTERN IN INFERTILE WOMEN"

Dr. Nida Ansari — Junior Resident, Department of Obs. and Gynae, M.L.N. Medical College Prayagraj

Dr. Amita Yadav* — Assistant Professor, Department of Obs. and Gynae, M.L.N. Medical College Prayagraj *Corresponding Author

Dr. Nishita Chaudhari — Junior Resident Department of Obs. and Gynae, M.L.N. Medical College Prayagraj

ABSTRACT **Objective:** To "Study the correlation of Hyperprolactinemia, Thyroid Disorders And Menstrual Pattern in Infertile Women"

Method :- The present study was conducted on 100 women (50 infertile women and 50 fertile women) attending the outpatient and inpatient Department of Obstetrics and Gynaecology in associated hospitals of MOTI LAL NEHRU MEDICAL COLLEGE PRAYAGRAJ over a period of twelve months during the year 2018-2019. Taking all aseptic and antiseptic precautions, 5 milliliters of fasting venous sample was obtained in the morning of day3 of menstrual cycle for serum biochemical analysis. Serum was separated and stored for further analysis. Estimations of serum prolactin, Serum FT3, FT4, TSH are done by using BIO-RAD 680 ELISA microplate reader version 1.7 . The incidence of hyperprolactinaemia and thyroid disorders and menstrual irregularities was studied. The association between thyroid dysfunction, levels of serum prolactin and menstrual status were reviewed.

Results:- The majority of the infertile and fertile women were euthyroid and had normal prolactin level. In infertile group, the prevalence of hypothyroidism and hyperprolactinemia was slightly higher in the infertile group in comparison with that of the fertile group. There was a positive correlation between serum hypothyroidism and prolactin hyperprolactinemia in the infertile subjects (06%). P= <0.05. Hyperprolactinemia was depicted in 28% of the infertile women and hypothyroidism was found in 22%. Menstrual complaints were found in 54% cases

Conclusions:- In this study there is a positive correlation between increased prolactin levels and hypothyroidism and such patients' exhibit ovulatory failure. All patients with infertility should undergo prolactin levels and thyroid profile. . Problems in infertility are challenging and taxing to the clinician which can be solved just by tackling some simple endocrinological conditions like hyperprolactinaemia and thyroid disorders.

KEYWORDS : Hypothyroidism, Hyperprolactinemia, Menstrual irregularity

INTRODUCTION

Hormonal disorders of female reproductive system comprise of a number of problems resulting from aberrant dysfunction of hypothalamic-pituritary-ovarian axis. These relatively common disorders often lead to infertility. Failure to conceive following 1 year of regular intercourse without the utilization of contraception is defined as infertility that can be either primary or secondary. Fertility declines with age, female fertility is at its peak between the ages of 18 and 24 years, while it begins to decline after the age of 27 age and drops at a somewhat greater rate after age 35.Pituitary hormones such as TSH, prolactin or growth hormone may act synergistically with FSH and LH at enhance the entry of non-growing follicles into the growth phase **Alaa Shaker Al-Nahi et al (2014).**

Thyroid hormone is important for growth and metabolism. It regulates cellular functions, therefore along with gonadotropins, e.g. follicular stimulating hormone (FSH), luteinizing hormone (LH) and prolactin also play an important role in female system and fertility **Nazlima Nargis et al (2018).** Thyroid dysfunction which is quite prevalent in the population affects many organs including male and female gonads, interferes with human reproductive physiology, which reduces the likelihood of pregnancy and adversely affects pregnancy outcome, thus becoming relevant in the algorithm of reproductive dysfunction.

Prolactin, a 198-amino acid polypeptide secreted by the anterior pituitary lactotroph, is the primary trophic factor responsible for synthesis of milk by the breast. Hyperprolactinemia is an endocrine disorder involving hypothalamic–pituitary axis that results from multiple causes, including medications, hypothyroidism, and pituitary disorders. Prolactin (PRL) secretion is inhibited by PRL inhibitor factor that is secreted from hypothalamus, enhanced by dopamine antagonism and thyroid-releasing hormone (TRH).

Hyperprolactinemia adversely affects the fertility potential by impairing pulsatile secretion of GnRH and hence interfering with ovulation. This disorder has been implicated in menstrual and ovulatory dysfunctions like amenorrhea, oligomenorrhea, anovulation, inadequate corpus luteal phase and galactorrhea **Mishra R et al (2002)[4].**

Hyperprolactinaemia and Hypothyroidism are found to be closely inter-related.Primary hypothyroidism is characterized by low serum level of thyroxine (T4) and decreased negative feedback on the hypothalamo-pituitory axis. The resulting increased secretion of thyrotropin releasing hormone (TRH) stimulates thyrotrophs and lactotrophs, thereby increasing the levels of both thyroid stimulating hormone and prolactin **Shoupe D et al (1997)[5].**

Hyperprolactinemia which results from a longstanding primary hypothyroidism may result in ovulatory dysfunctions ranging from inadequate corpus luteal progesterone secretion to oligomennorhoea or ammenorhoea. Amenorrhoea occurs in hypothyroidism due to hyperprolactinaemia, which results from a defect in the positive feedback of oestrogen on LH, and because of the suppression of LH and FSH.

Aims and Objective

1. To study the prevalence of hyperprolactinemia and thyroid disorders
2. To study the correlation between thyroid disorders and hyperprolactinemia in infertility cases
3. Menstrual pattern in infertile women with thyroid disorders and hyperprolactinemia.

MATERIALS AND METHOD

To **"STUDY THE CORELATION OF HYPERPROLACTINEMIA, THYROID DISORDERS, OVARIAN RESERVE AND MENSTRUAL PATTERN IN INFERTILEWOMEN"** 100 women attending outpatient department as well as those admitted in Gynecology wards in Swaroop Rani Nehru Hospital and Kamla Nehru Memorial Hospital, Department of Obstetrics and Gynaecology, Motilal Nehru Medical College, Prayagraj, were enrolled over a period of one year from September 2018 to august 2019. The study was conducted in two broad groups as follows:-

1. STUDY GROUP–This group included 50 female patients 20-40 years of age with either primary or secondary infertility.
2. CONTROL GROUP- This group included age matched 50 fertile patients.

A written informed consent was obtained from all subjects prior to the

performance of any study related procedure.

A Detailed clinical history was taken with special reference to age, Education, Occupation, Socioeconomic status, Residential area (rural/urban), Drug intake, Contraception use,Treatment received by husband, Coital frequency , Period of infertility, Seeking treatment for infertility and a known congenital anomaly in the patient Menstrual history was taken regarding -cycle, flow and duration, LMP (last menstrual period) association with pain in abdomen and passage of clots.

Obstetrical history was taken for – Duration of marriage, parity, previous abortion, mode of delivery, no of alive/dead infants

A past and family history was taken regarding diabetes mellitus, thyroid disorder pregnancy loss, thrombotic disorders and tuberculosis in any site or any operation on or near genital tract, any other previous illness and operations.

A detailed personal history was taken regarding eating habits addiction to tobacco, alcohol, caffeine, any contraception practiced or duration for which contraception has been practiced.

General examination a thorough general examination was done with special reference to General condition, pulse rate, blood pressure, temperature, respiratory rate, pallor, icterus, edema, lymphadenopathy, height, weight, body mass index Systemic examination a thorough systemic examination of central nervous, cardiovascular, respiratory, gastrointestinal system was done to diagnose any system specific disease. Examination of thyroid gland was done for any goiter or nodule and any other abnormality.

Selection of Cases

1. Fertile Female (20-40 Yrs)
2. Female with Primary or Seconday fertility

The Inclusion Criteria

1. Women with infertility, age between 20-40 years.
2. Duration of marriage more than 1 year.

The exclusion Criteria

1. Tubal factor
2. Congenital anomaly of the urogenital tract,or any obvious organic lesion.
3. Any history of thyroid disease or previous thyroid surgery or being on thyroid medications.

Method of determining S.prolactin, S. FT3, S. FT4, S.TSH & AMH Levels

Estimations of serum prolactin, Serum FT3, FT4, TSH are done by using BIO-RAD 680 ELISA microplate reader version 1.7 .

AMH levels were assessed in blood serum by a 2nd generation Beckman Coulter assay.

Observation

The present study was conducted to evaluate infertile women for menstrual pattern, endocrine status and ovarian reserve attending the outpatient and inpatient Department of Obstetrics and Gynaecology in associated hospitals of Moti Lal Nehru Medical college Prayagraj (i.e. Swaroop Rani Nehru Hospital and Kamla Nehru Memorial Hospital), in collaboration with the Department of Radiodiagnosis and Department of Pathology over a period of twelve months from September 2018 to August 2019.

A total of 100 subjects were recruited for the study aged 20 to 40 years, out of which 50 infertile women constituted the study group and 50 fertile women as control. All were subjected to detailed history, examination, routine investigations and specific investigations like thyroid profile, Serum prolactin, anti-mullerian hormone and ultrasonography

Table No. 1 Distribution on the basis of Demography

Variables	Control group		Study Group	
Age	**No. of cases**	**Percentage**	***No. of cases***	***Percentage***
20-25	16	32%	*13*	*26%*
26-30	23	46%	*25*	*50%*
31-35	06	12%	*10*	*20%*
36-40	05	10%	*02*	*04%*
Parity				
Nulliparous	00	00%	38	76 %
Primiparous	04	08%	09	18 %
Para 2	21	42%	03	06 %
Para 3	18	36%	00	00%
Para 4	04	08%	00	00 %
≥ Para 5	03	06%	00	00%
Education				
Illiterate	07	14%	06	12%
Primary	11	22%	10	20%
High School	15	30%	11	22%
Intermediate	10	20%	14	28 %
Graduate & Higher Education	07	14%	09	18 %
Socio Economics Status				
Urban	22	44%	29	58%
Rural	28	56%	21	42 %
Upper (Class I)	03	06%	03	06%
Upper middle (Class II)	15	30%	18	36 %
Lower middle (class III)	19	38%	15	30 %
Upper lower(class IV)	8	16%	09	18 %
Lower class (class V)	5	10%	05	10 %
Student	01	02%	02	04%
Office worker	07	14%	12	24%
Agriculture	11	22%	09	18%
Housewife	31	62%	27	54%
B M I				
< 18.5	01	02%	02	04%
18.5-24.9	24	48%	18	36%
25-29.9	18	36%	23	46%
30-34.9	06	12%	06	12%
>35	01	02%	01	02%

Table- 2 Distribution of cases of Study and control group according to thyroid Status

Thyroid profile	Euthyroid		Hypothyroidism		
	Control group	**Study group**	**Control group**	**Study group**	**P value**
No of cases (percentage)	45 (90%)	39 (78%)	05 (10%)	11 (22%)	0.101
Mean value of S. TSH (uIU/ml)	2.44±1.41	2.86±1.03	7.89±2.08	15.72±27.9	
Mean value of T3 (pg/ml)	2.22±0.76	2.08±0.85	1.69±0.69	2.01±1.21	
Mean value of T4 (ng/ml)	1.02±0.29	0.93±0.16	0.87±0.08	0.87±0.15	

Table- 3 Distribution of cases of control and study group according to prolactin level

	Normal prolactin level		Hyperprolactinemia		
Serum prolactin level	**Control group**	**Study group**	**Control group**	**Study group**	**P-value**
No of cases	46 (92%)	36 (72%)	04 (08%)	14 (28%)	0.009
Mean value (ng/ml)	11.85±5.36	11.70±5.47	38.96±4.34	56.13±51.70	

Table 4 -Co-existence of thyroid status and hyperprolactinemia in control and study group

Thyroid profile / prolactin level	Control group			Study group		
	Euthyroid	**Hypo- thyroid**	**Total**	**Euthyroid**	**Hypo- thyroid**	**Total**
	No of cases (percentage)	**No of cases (percentage)**		**No of cases (Percentage)**	**No of cases (Percentage)**	
Normal prolactin	41(82%)	5(10%)	**46**	28(56%)	08(16%)	36

Hyperpro-lactinemia	4(08%)	0(00%)	**04**	11(22%)	03(06%)	14
TOTAL	**45(90%)**	**5(10%)**	**50**	**39(78%)**	**11(22%)**	**50**
P value	**0.017**			**0.013**		

Table 5 -Menstrual pattern in control and study group with thyroid disorders

Symptoms	Euthyroid		Hypothyroidism	
	Study group	Control group	Study group	Control group
Regular pattern	18	38	05	01
Scanty menses	04	04	01	01
Heavy menstrual bleeding	00	01	00	00
Frequent cycle	00	00	01	01
Infrequent cycle	07	02	02	00
Scanty+Infrequent cycle	10	00	01	02
HMB+frequent cycle	00	00	01	00
HMB+ Infrequent cycle	00	00	00	00
Total	**39**	**45**	**11**	**05**
P value	0.4			
	0.0002	**0.50**		

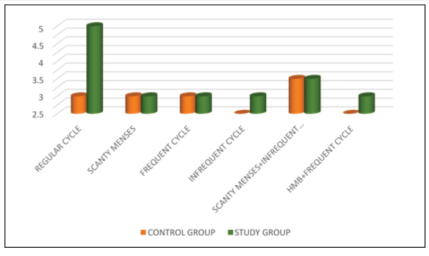

Figure 1-Bar diagram showing menstrual pattern in cases with thyroid disorders

Table 6- Menstrual pattern in control and study group with hyperprolactinemia

Symptoms	Normal prolactin		Hyperprolactinemia	
	Control group	Study group	Control group	Study group
Regular pattern	37	18	02	05
Scanty menses	04	03	01	02
Heavy menstrual bleeding	01	00	00	00
Frequent cycle	01	00	00	01
Infrequent cycle	02	06	00	03
Scanty+Infrequent cycle	01	09	01	02
HMB+frequent cycle	00	00	00	01
HMB+ Infrequent cycle	00	00	00	00
Total	**46**	**36**	**04**	**14**
P value	0.202			
	0.005		0.06	

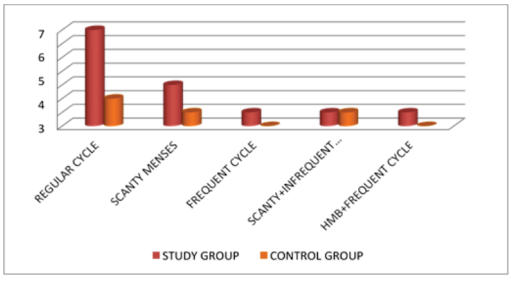

Figure2-Bar diagram showing menstrual pattern in casesh hyperprolactinemia

Table 7- Mean hormonal status in study and control group

	Control group	Study group	P Value
Parameters	Mean ± SD	Mean ± SD	
S. TSH (uIU/ml)	2.84 ± 2.13	5.69 ± 13.77	0.015
S. free T3 (pg/ml)	2.16 ± 0.76	2.07 ± 0.93	0.59
S. free T4 (ng/ml)	1.00 ± 0.28	0.92 ± 0.16	0.08
S. Prolactin (ng/ml)	14.02 ± 9.09	24.14 ± 33.71	0.04

DISCUSSION

In this study, 58% patient were of primary infertility and 42 were of secondary infertility. Mean age in infertile group was 27.9±4.13 and mean BMI was 25.12± 3.89. The majority of infertile as well as fertile women were euthyroid and had normal prolactin levels but hypothyroidism and hyperprolactinemia both were more prevalent in infertile group.

In present study the subjects with regular cycles and with menstrual complaints were 46% and 54% respectively. These results were comparable to the study conducted by **Avasthi et al (2006)** which had similar pattern of cycles. 42% cases had Regular cycles and menstrual abnormalities were present in 58% of cases, **Goswami B et al (2009)** found 61% women with menstrual irregularities.

The prevalence of hypothyroidism was 05(10%) in control group while in study group prevalence was 11(22%). Similar percentage of hypothyroidism was observed in study by **Verma I et al (2011)**23.9%, **Alaa Shankar et al (2014)** 20.4%. In present study, lower occurrence of hyperprolactinemia 04(08%) was seen in the control group as compared to the study group 14(28%). Incidence of hyperprolactinemia in study by **Alaa Shaker Al-Nahi et al (2014)** was 29.5% which was similar to this study. In study by **Avasthi K et al(2006)** it was 46%, , **Goswami et al (2009)** study 41% Co-existence of hypothyroidism and hyperprolactinemia in this study was found in 06% cases. P= <0.05 . Therefore there is significant association between thyroid profile and hyperprolactinemia. In a study by **Verma I et al (2012)** 4.47% which was similar to present study While in study by **Nallusamy S et al (2016)** 25.5% and in **Sharma P et al (2017)** 17.07% which were higher.

In study group out of 11 cases of hypothyroidism 5(45.5%) had regular pattern and 6(54.5%) had irregular menstrual pattern and in hyperprolactinemia group 64.2% cases had menstrual irregularity.

CONCLUSION

There was a higher incidence of hypothyroidism and hyperprolactinemia in the infertile women as compared to the fertile ones in the control group. 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. Problems in infertility are challenging and taxing to the clinician which can be solved just by tackling some simple endocrinological conditions like hyperprolactinaemia and thyroid disorders.The problem of infertility is seen in women with higher age groups due to the trend of late marriages. Presence of hyperprolactinaemia should be looked for in subjects with oligomenorrhoea, amenorrhoea

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