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Female Infertility Risk Assessment in Relation to Serum Thyroid Hormone Levels and Serum Prolactin Levels

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Abstract

***Background**: Female infertility is an important problem with psychological and social implications. Existence of thyroid dysfunction and prolactin levels are considered an important cause of infertility in otherwise normal females. Hypothyroidism is known to affect fertility because it leads to anovulatory cycles, luteal phase defects, hyperprolactinemia, and sex hormone imbalances. **Aim**: We in the current study tried to evaluate the prevalence of clinical/sub-clinical hypothyroidism along with the presence of serum prolactin disorders in females with infertility. **Methods**: Women with primary or secondary causes of infertility attending the Department of Obstetrics and Gynecology were enrolled for the study. Age-matched women were included as controls. Fasting blood samples were obtained in the follicular phase and serum TSH, FT4, and FT3 were estimated by enzyme-linked immunosorbent assay and PRL levels were estimated by RAI. **Results**: The mean TSH levels of women with primary and secondary infertility were found to be significantly higher than the control group III. Similarly, the mean FT4 levels of the women with primary and secondary infertility (Group I and Group II) were significantly lower than the control group III. The mean serum levels of FT3 were not significantly different between all the groups. The mean serum prolactin levels of women in the group I and group II were significantly higher the control group III. **Conclusion**: Thyroid abnormalities are very common in females and chronic hypothyroidism may lead to ovulatory dysfunctions and hyperprolactinemia. Identifying and treating hypothyroidism is critical for normal ovulatory functions and fertility. We found that the presence of hypothyroidism increases the risk of infertility. Therefore, thyroid screening for females must be an important part of an infertility workup.*

***Keywords**: Female Infertility Risk Assessment, Thyroid hormones, Prolactin*

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Introduction

Approximately 85% of normal couples will conceive after regular and unprotected sexual intercourse within a period of 12 months. Infertility is diagnosed when there is a failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse. [1] The term primary infertility is used in cases who have never achieved a pregnancy despite regular sexual intercourse and secondary infertility is used for the couples who have achieved at least one pregnancy even if it has ended by miscarriage/abortion. Across the world, approximately 8–12% of couples experience some form of infertility during their reproductive lives. [2, 3] The female factors contributing to infertility includes aberrant functions of the hypothalamic-pituitary-ovarian axis. In 30% of cases, male factor contributes to infertility and 35% of cases female factors are involved and combination of both are found in 20% of infertility cases and 15% are idiopathic causes. [4] Fertility is at the peak from 20 – 25 yrs of age and decreases relatively little until approximately the age of 30 – 32 years.

Thereafter declines progressively, more rapidly after the age of 40 years, as well as an increased chromosomal abnormality or other malformed fetuses. Therefore, it is prudent to proceed with investigations after 6 months of apparent infertility in women near or over the age of 35 years. The neuroendocrinal relationship between TSH and Prolactin is thyrotropin-releasing hormone (TRH), which stimulates the secretion of both TSH & Prolactin. [5] TRH is under negative feedback control of TSH through a short negative feedback loop, any increase in TSH will decrease the release of TRH which in turn will inhibit the secretion of prolactin & will also normalize the TSH levels. A prominent feature of the hormonal cascade is the negative feedback system operating when sufficiently high levels of the ultimate hormone have been secreted into the circulation. The short feedback loop is exemplified by the pituitary hormone that feeds back negatively (TSH in this case) on the hypothalamus operating through a cognate receptor. [6] PRL secretion is under dual regulation by hypothalamic hormones via the pituitary portal circulation. Hypothyroidism is linked to infertility because for optimum production of estradiol and progesterone adequate functioning of the thyroid gland is important. [7, 8] With this background we in the present study undertook the evaluation of thyroid hormone and prolactin levels in women presenting to our hospital with infertility.

Materials and Methods

This prospective cross-sectional study was conducted in the Department of Obstetrics and Gynecology, Narayana Medical College and Hospital, Nellore. Institutional Ethical Committee clearance was obtained for the study after the submission of the protocol of the study to the Ethical committee. The study period was from June 2018 to May 2019 (12 Months) Written consent was obtained from all the participants of the study. The patients were selected from those reporting to OBG OPD with complains of infertility. Primary infertility was diagnosed when the women have never conceived. Secondary infertility was denoted when there was an initial phase of fertility when she conceived previously however, failed to conceive thereafter. Primary or secondary infertility, women with husbands having normal semen analysis, women with normal genitalia, uterus, and adnexa were included in the study while those with congenital anomaly of the urogenital tract, PID, tubal factors, and PCOD were excluded.

A total of 90 women were included in the study. Out of which n=30, were diagnosed with primary infertility included in group I, n=30, were diagnosed with secondary infertility included in group II and n=30 were age-matched controls. A detailed history including medical, drugs, personal, family history was recorded. The patients were subjected to a detailed clinical examination which includes a general examination, systemic examination, and pelvic examination was done. Estimation of serum TSH, FT4, FT3 was done using ELISA while serum Prolactin was estimated by RAI. The normal range of TSH was 0.3 – 0.4 mIU/L, FT4 was 10.3-24.5 pmol/L, FT3 was 2.3-6.3 pmol/L and Prolactin was 2-25 ng/ml. The statistical analysis was performed by IBM SPSS Statistics 20 version Categorical variables are described as frequency, percentage, and Chi-square test for p values ($p<0.05$ was considered significant).

Results

The age range was from 22.5 years to 33 years. The mean ages of all groups were found to be similar and statistically insignificant. The BMI was measured for all the women. The mean BMI of group I was 27.5 Kg/m^2 and group II was 26.9 Kg/m^2. The values between group I and group II were found to be statistically insignificant. The mean BMI of group III (controls) was 24.55 Kg/m^2. A comparison of BMI between group I and group III were found to be ($p <0.05$) significant. Similarly, the comparison of group II versus group III for BMI results ($p <0.04$) which was statistically significant.

The mean serum levels of TSH, FT4, FT3, and prolactin of groups I, II, and III are shown in table 1.

Analysis by one-way ANOVA was done between the Primary infertility group I versus normal controls group III and similarly, between-group II secondary infertility and control Group III. The mean TSH levels of women with primary and secondary infertility were found to be significantly higher in the

control group III. Similarly, the mean FT4 levels of the women with primary and secondary infertility (Group I and Group II) were significantly lower than the control group III. The mean serum levels of FT3 were not significantly different between all the groups. The mean serum prolactin levels of women in group I and group II were significantly higher in the control group III (Table 2).

Table 1: Serum TSH, FT4, FT3 & prolactin levels

Study Population	No. of cases (n)	Mean ± SD			
		TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)	Prolactin (ng/ml)
Group I	30	5.19 ± 0.74	9.84 ± 0.87	4.01 ± 0.31	15.28 ± 1.73
Group II	30	6.95 ± 0.64	7.88 ± 0.49	3.87 ± 0.21	15.96 ±1.10
Group III	30	1.89 ± 0.22	15.11 ± 0.71	5.01 ± 0.29	10.50 ± 0.65

Table 2: One-way ANOVA analysis of the cases in various groups

ANOVA	TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)	Prolactin (ng/ml)
	Group III	**Group III**	**Group III**	**Group III**
Group I	0.05*	0.02*	0.353	0.0478*
Group II	0.012*	0.032*	0.15	0.002*

* significant

Table 3: Thyroid function status and prolactin levels

Study groups	Number (%)	Mean ± SD TSH (mIU/L) levels	Mean Serum Prolactin levels	
			High	Normal
Group I (n=30)				
Euthyroid	12 (40)	3.98 ± 0.32	4(33.33)	8(66.67)
Hypothyroid	18 (60)	5.56 ± 0.77	8(44.4)	10(55.56)
Hyperthyroid	0	-	-	-
Group II (n=30)				
Euthyroid	11(36.67)	4.15 ± 0.59	3(27.27)	8(72.72)
Hypothyroid	19 (63.33)	6.69 ± 1.15	7(36.84)	12(63.15)
Hyperthyroid	0	-	-	-
Group III (n=30)				
Euthyroid	30 (100)	2.12 ± 0.21	0	30(100)

In this study based on thyroid functions, 60% of group I females and 63.33% of group II females were found to be hypothyroid. No case of hyperthyroid was detected in either group. All the cases of the control group were euthyroid. The mean TSH levels in group I and group II were found to be higher in both groups compared to the control group. Normal prolactin levels were found in n=10(55.56%) of hypothyroid patients of group I and 12(63.15%) of cases of group II (table 3)

The odds ratio calculated for the group I hypothyroid patients was found to 1.5 and the odds ratio for hyperprolactinemia was 0.66. This indicates that hypothyroid patients have greater chances of infertility as compared to prolactin levels. Similarly, for Group II, the odds ratio for hypothyroidism was 1.72, and the odds ratio for hyperprolactinemia was 0.5.

Table 4: Odds ratio for hypothyroidism and Hyperprolactinemia in study groups

	Odds ratio	
	Hypothyroidism	**Hyperprolactinemia**
Group I	1.50	0.66
Group II	1.72	0.50

Discussion

The existence of Hypothyroidism is common, with overt hypothyroidism affecting 0.5% of women of reproductive age. Mild Thyroid failure or Subclinical hypothyroidism has a prevalence of approximately 2–4% and is characterized by raised serum Thyroid-

stimulating hormone (TSH) levels of more than 4.5 mIU/l in combination with a normal FT_4 and no clinical symptoms or signs of hypothyroidism. [9] Hypothyroidism is known to affect the pulsatile release of Gonadotrophin-releasing hormone, which is required for cyclical release of Follicle-stimulating hormone and Luteinizing hormone and subsequent ovulation. Hypothyroidism in childhood and adolescence is associated with a delay in reaching sexual maturity, and in adulthood is associated with menstrual disturbances (particularly oligomenorrhoea, menorrhagia, and amenorrhoea) and in some cases anovulation. [10] In this study we found that high prolactin levels were found in n=8(44.4%) of cases of primary infertility and n=7(36.84%) of cases with secondary infertility. High prolactin levels are some of the biochemical abnormalities, particularly in infertile females. [9] The prolactin is said to affect the ovaries by altering ovarian progesterone secretion and estrogen synthesis causing infertility. [9, 10] The women with high prolactin may ovulate regularly but do not produce enough progesterone during the luteal phase of ovulation. Due to the lower quantity of progesterone embryo implantation and subsequent development is hampered. Studies have shown that long-standing primary hypothyroidism leads to hyperprolactinemia which has been implicated in ovulatory dysfunctions. [10] The current study found that the odds ratio for hypothyroidism in cases of primary infertility was 1.5 and the odds ratio of hypothyroidism in secondary infertility was 1.72 indicating the infertility risk is higher in both groups as far as hypothyroidism is concerned. However, the study shows that the odds ratio for primary infertility in cases of hyperprolactinemia was 0.66 and in secondary infertility, it was 0.5. These results are consistent with statements made before that long-term hypothyroidism can lead to hyperprolactinemia which then results in ovulatory dysfunctions. The odds ratio for hyperprolactinemia was lesser because it takes time for hyperprolactinemia to develop after exposure to lower levels of thyroid hormones. Hypothyroidism may also alter feedback to the pituitary by changing estrogen metabolism and circulating levels of sex hormone-binding globulin. There is evidence of a dose-dependent association, with women with higher serum TSH levels having greater menstrual disturbance and anovulatory cycles. [11] Women presenting with infertility also appear to have raised mean serum TSH levels and increased rates of subclinical and overt hypothyroidism compared with controls. This is compounded by an increase in T_4 binding to Thyroxine-binding globulin in response to rising estrogen levels as a result of controlled ovarian hyperstimulation, potential. [12] There is a suggestion that raised levels of serum TSH may be associated with reduced rates of fertilization during assisted conception and reduced pregnancy rates overall in women with a serum TSH of more than 2.5 mIU/l. [13] Improvements in implantation, pregnancy and live birth rates have been reported following treatment with levothyroxine (LT_4) in those with overt, and clinical hypothyroidism. However, even following thyroid replacement therapy, egg numbers and fertilization rates, and implantation, pregnancy and live birth rates appear to be reduced compared with euthyroid controls. [12] based on this evidence there has been a recent shift in practice to maintain serum TSH levels below 2.5 mIU/l pre-conceptually in the infertility setting, in line with the American Thyroid Association guidelines for first-trimester serum TSH. [14] Therefore, TSH and prolactin are commonly ordered clinical tests in evaluating infertile women.

Conclusion

Thyroid abnormalities are very common in females and chronic hypothyroidism may lead to ovulatory dysfunctions and hyperprolactinemia. Identifying and treating hypothyroidism is critical for normal ovulatory functions and fertility. We found that the presence of hypothyroidism increases the risk of infertility. Therefore, thyroid screening for females must be an important part of an infertility workup.

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