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Original Research Article

Study of Primary and Secondary Infertility in Women with Hypothyroidism and Hyperprolactinemia

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Abstract:

Background: India is not the only country with infertility issues. Infertility is thought to be a result of altered thyroid and prolactin levels. The goal of the study was to determine whether women with primary and secondary infertility had elevated levels of prolactin and serum thyroid hormones.

Methods: The participants included both primary and secondary infertile women. Age-matched, fertile women served as the control group. Age, height, and weight anthropometric data were noted. On the second day of the follicular phase of the menstrual cycle, an overnight fasting blood sample was taken. By using an enzyme-linked immunosorbent assay (ELISA), the levels of serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were assessed. A radioimmunoassay was used to determine the serum prolactin (PRL).

Results: 150 women in all were enrolled in the trial. Out of 150 women, 50 experienced primary infertility, 50 secondary infertility, and 50 were fertile women of a similar age who served as the control group. Both infertility groups had significantly higher mean TSH levels than women who were fertile. In terms of thyroid function, hypothyroidism was seen in 24% and 28% of women with primary and secondary infertility, respectively. In the primary and secondary infertility groups, elevated serum prolactin levels were seen in 42.9% and 50% of hypothyroid patients, respectively.

Conclusion: The study has highlighted the significance of measuring both serum TSH and prolactin in infertility by showing a high prevalence of hypothyroidism with elevated serum prolactin levels among infertile females.

Introduction

In India, infertility is a significant public health issue. India's fertility rate was 2.2 births per woman in 2020. From 5.5 births per woman in 1971 to 2.2 births per woman in 2020, India's fertility rate gradually decreased [1-4]. Infertility and thyroid function changes are linked [5–13]. It has been thought that thyroid hormones, particularly thyroid stimulating hormone (TSH), have a significant role in infertility. It has been discovered that women with hyperprolactinemia had primary hypothyroidism. Numerous elements of pregnancy and reproduction are impacted by thyroid dysfunction. The link between hypothyroidism or hyperthyroidism and menstrual irregularities, anovulatory cycles, lower productivity, and higher morbidity during pregnancy has been noted in a number of articles [8–10,14,15]. Since thyroid hormones are required for the optimum generation of both estradiol and progesterone, hypothyroidism alone may lead to infertility [12,13]. Therefore, it is essential to test prolactin and serum thyroid hormones in women who are having infertility issues. Therefore, the goal of the current study was to assess the thyroid function of infertile women.

Material and Methods

From September 2021 to August 2022, the current study was carried out at the Department of Obstetrics and Gynecology in collaboration with the Department of Biochemistry, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, The study included both primary and secondary infertile women. As a control group, an equal number of women who appeared to be fertile and in good health were enlisted. Women who are primary infertile are individuals who have never

given birth. According to one definition, secondary infertility is the same condition that develops after the original phase of fertility, meaning the woman became pregnant initially but was unable to become pregnant again[12].

The ability to conceive was used to characterize fertility. Women who are infertile and whose husbands have normal semen analyses as well as those whose genitalia, uteruses, and adnexa are normal were included. Only primary hypothyroidism and primary hyperthyroidism were included in this study; women with tubal factor, congenital anomaly of the urogenital tract, any obvious organic lesion, pelvic inflammatory diseases, lactating women, and infertile women with subclinical hypothyroidism, secondary hypothyroidism, and secondary hyperthyroidism were excluded. Each participant received a thorough explanation of the study's goals and advantages before providing their written consent. In a pre-designed questionnaire, a thorough medical, drug, personal, familial, and socio-economic histories were documented.

Each participant's cubital vein was used to collect 5 milliliters of blood aseptically. The blood was centrifuged at 3000 rpm for 5–10 minutes after being allowed to clot for 30–60 minutes at room temperature. For the purpose of estimating serum TSH, FT4, FT3, and prolactin, the serum was isolated and stored at -20^{0}C. Radioimmunoassay was used to assess blood prolactin levels, and enzyme-linked immunosorbent assay (ELISA) was used to measure thyroid hormones. The analysis was completed two weeks after the blood was collected. TSH, FT4, FT3, and prolactin all fell within the normal range of 0.3-4.0 mIU/L, 10.3-24.5 pmol/L, 2.3-6.3 pmol/L, and 2-25 ng/ml, respectively.

The study population was divided into three groups: euthyroidism (when TSH and FT4 values were within the normal range), hypothyroidism (when TSH exceeded 4.0 mIU/L and FT4 was normal or low), and hyperthyroidism (when TSH was less than 0.1 mIU/L or undetectable and FT3 or FT4 values were normal or elevated)[16,17].

The proper statistical tests, including one-way ANOVA, Tukey's HSD post-hoc test, unpaired student's t test, and Z test, were used to examine the data.

Results

The study involved 150 female participants in total. 50 of the 150 participants had primary (Group A) and 50 had secondary (Group B) infertility. As a control (Group C), 50 age-matched, ostensibly fertile women were enlisted. The study population ranged in age from 23 to 34 years old, and no statistically significant differences were found between the mean ages of the various groups. The mean body mass index (BMI) between Groups A and B did not significantly differ.

Table 1 displays the mean serum levels of TSH, FT4, FT3, and prolactin in Groups A, B, and C. Women with primary (4.83±0.54 mIU/L) and secondary (6.40±0.59 mIU/L) infertility had mean serum TSH levels that were considerably ($p<0.001$) greater than women with normal fertility (1.98±0.18 mIU/). Women with primary (10.54±0.66 pmol/L) and secondary (7.64±0.44 pmol/L) infertility had median blood FT4 levels that were considerably ($p<0.005$) lower than women with normal fertility (14.48±0.64 pmol/L).

Women with primary (4.12±0.32 pmol/L) and secondary (3.9±0.23 pmol/L) infertility had mean serum FT3 levels that were considerably ($p=0.03$ and $p=0.001$) lower than women with normal fertility (4.93±0.20 pmol/L). Serum FT3 levels did not significantly differ between Groups A and B. those with primary (14.54±1.23 ng/ml) and secondary (15.36±1.02 ng/ml) infertility had substantially higher mean serum prolactin levels than those with normal fertility (10.58±0.71 ng/ml) ($p <0.05$). Women with primary and secondary infertility did not show any discernible differences.

Table 1: Serum TSH, FT4, FT3 and prolactin levels of study population

Study Population	No.	Mean±SE serum level of			
		TSH (mIU/L)	FT4 (pmol/L)	FT3 (pmol/L)	Prolactin (ng/dl)
Group A	50	4.83±0.54	10.54±0.66	4.12±0.32	14.54±1.23
Group B	50	6.40±0.59	7.64±0.44	3.9±0.23	15.36±1.02
Group C	50	1.98±0.18	14.48±0.64	4.93±0.20	10.58±0.71

Note: GrA = Primary infertility, GrB = Secondary infertility, GrC = Control; For TSH – GrA vs GrC: $p<0.001$, GrB vs GrC: $p<0.001$, GrA vs GrB: $p = 0.05$; For FT4 – GrA, GrB and GrC were significantly different from each other: $p<0.005$; For FT3 – GrA vs GrC: $p = 0.03$, GrB vs GrC: $p = 0.001$, GrA vs GrB: $p = 0.58$; For prolactin – GrA vs GrC: $p = 0.017$, GrB vs GrC: $p = 0.003$, GrA vs GrB: $p = 0.834$. One way ANOVA and Tukey's post-hoc tests were performed to compare among the groups.

According to the thyroid function status, 28% and 24% of women with primary infertility and 28% and 72% of women with secondary infertility, respectively, were hypothyroid (Table 2). Women in the control group were all thyroidally normal. In 2% and 4% of women with primary and secondary infertility, respectively, there was primary

hyperthyroidism (Table 2). When compared to the hypothyroidism cases in the initial infertility group (5.14± 0.85 mIU/L), the mean serum TSH level in the secondary infertility group (7.97±0.72 mIU/L) was substantially higher (p=0.02). In 42.9% and 50% of cases with hypothyroidism in women with primary and secondary infertility, high serum prolactin levels were seen.

Table 2: Thyroid function status and prolactin levels in women with primary and secondary infertility

Study population	Number (%)	Mean±SE serum TSH (mIU/L)	Serum Prolactin level	
			High N(%)	Normal N(%)
Group A (n=50)				
Euthyroid	35(70)	3.12±0.21	2(5.7)	33(94.3)
Hypothyroid	14(28)	5.14±0.85	6(42.9)	8(57.1)
Hyperthyroid	1(2)	-	0	1(100)
Group B (n=50)				
Euthyroid	36(72)	4.12±0.16	1(2.7)	35(97.3)
Hypothyroid	12(24)	7.97±0.72	6(50)	6(50)
Hyperthyroid	2(4)	1.07±1.04	0	2(100)
Group C (n=50)				
Euthyroid	50(100)	1.98±0.18	0	50(100)

Note: High prolactin = >25 ng/ml; Z test was performed; GrA vs GrB with euthyroid: Z = 0.82, p = 0.22; GrA vs GrB with hypothyroid: Z = 0.45, p = 0.54; GrA vs GrB with hyperthyroid: Z = 0.580, p = 0.55.

In primary and secondary infertile women, the Pearson's correlation coefficient was measured for serum TSH and prolactin. Serum prolactin levels and concomitant TSH levels were substantially associated in primary infertile women (r = 0.941, p <0.001). Serum prolactin levels and serum TSH levels substantially correlated in secondary infertile women (r=0.915, p< 0.001). As a result, a substantial correlation between hyperprolactinemia and hypothyroidism was found in both primary and secondary infertile women.

Discussion

Female infertility has been linked to thyroid issues and changes in prolactin levels[8-10,15,18-23]. In the current study, primary and secondary infertility were detected in 24%–28% of the women who also had hypothyroidism. Numerous studies[8-15,18,20-22,24] have identified similar thyroid dysfunction patterns. Increased thyrotropin-releasing hormone (TRH) production in hypothyroidism increases the release of prolactin and TSH, which results in hyperprolactinemia and altered gonadotropin-releasing hormone (GnRH) secretion[23]. Due to inadequate corpus luteum and delayed luteinizing hormone (LH) response, this causes aberrant follicular development and ovulation[8-15,18,20-24]. The most frequent biochemical anomaly associated with infertility is high prolactinemia[25]. Prolactin may also impact the ovaries, affecting their ability to produce estrogen and secrete progesterone, which can result in infertility[23,25]. Despite having frequent ovulation, women with high prolactin levels may not create enough progesterone during the luteal phase after ovulation. Lack of progesterone, which is released after ovulation, may prevent an embryo from implanting properly in the uterine lining [26,27]. Ovulatory dysfunction has been linked to long-term primary hypothyroidism-induced hyper prolactinemia [23].

If hypothyroidism and hype rprolactinemia are present in infertile females, the hypothyroidism should be treated first and TSH should be kept at the lower limit. The hypothalamic-pituitary-ovarian axis (HPO) and the hypothalamic-pituitary-thyroid axis (HPT) appear to be closely related in experimental and clinical studies[13,26–28]. This is due to the fact that some thyroid hormone receptors at the ovarian level may regulate estrogen effect as well as reproductive function at higher levels of the HPT axis, hence integrating the reciprocal link between these two major endocrine axis[24]. Patients with hyperprolactineemia who do not exhibit any signs of pituitary malfunction typically have low thyroid hormone levels.

We discovered that hyperprolactinemia was present in around 50% of our hypothyroid patients. Others have made similar observations and reported them[7,8,15,20,29-31]. Therefore, the present study has demonstrated that a significant number of women with primary and secondary infertility have altered thyroid function and serum prolactin levels compared to fertile women.

Conclusion

The study has demonstrated the need of evaluating serum prolactin and TSH in cases of infertility by demonstrating a significant incidence of hypothyroidism with higher serum prolactin levels in cases of infertile females.

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