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ORIGINAL RESEARCH

To study prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism in pregnancy

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ABSTRACT

Introduction: Prevalence of hypothyroidism is 2–4% in women in the reproductive age group. Hypothyroidism can affect fertility due to anovulatory cycles, luteal phase defects, hyperprolactinemia, and sex hormone imbalance. **Aims and Objectives:** To study the prevalence of hypothyroidism in infertile women and the response of treatment for hypothyroidism on infertility. **Material & methods:** A total of 120 infertile women of Department of Obstetrics and Gynaecology at Government medical college, Jammu & Kashmir were investigated for thyroid stimulating hormone (TSH) and prolactin (PRL). Infertile women with hypothyroidism alone or with associated hyperprolactinemia were given treatment for hypothyroidism with thyroxine 25–150 µg. The statistical analysis was done using IBM SPSS 24.0 software. **Results:** Of 120 infertile women, 57.5% were hypothyroid (TSH > 4.6 µIU/ml). After the treatment with thyroxine, 37.6% of subclinical hypothyroid women conceived within 6 weeks to 2-year period. The mean time to conception was 14.56 ± 4.83 months. After treatment for hypothyroidism, 69.5% of infertile women conceived 6 weeks to 1 year. Infertile women with both hypothyroidism and hyperprolactinemia also responded to treatment and their PRL levels returned to normal. **Conclusion:** Measurement of TSH and PRL should be done at early stage of infertility Check-up rather than straight away going for more costly tests or invasive procedures. Simple, oral hypothyroidism treatment for 3 months to 1 year can be of great benefi t to conceive in otherwise asymptomatic infertile women.

Keywords: Hypothyroidism, infertility, subclinical, treatment

INTRODUCTION

Infertility is a world health issue affecting approximately 8–10% of couple's worldwide.[1] WHO estimates the overall prevalence of primary infertility in India to be 3.5–16.8%.[2] Undiagnosed and untreated thyroid disease can be a cause for infertility as well as sub-fertility. Both these conditions have important medical, economical, and psychology implications in our society. Thyroid dysfunction is more common (4–5 times) in females than in males. Both hyperthyroidism and hypothyroidism have profound effects on estrogen and androgen metabolism, menstrual function and fertility.[3] They may cause delayed onset of puberty, menstrual abnormalities, anovulatory cycles, miscarriages and infertility. [4,5] Therefore, normal thyroid function is necessary for fertility, pregnancy, and to sustain a healthy pregnancy, even in the earliest days after conception.

Prevalence of hypothyroidism in the reproductive age group ranges from 2% to 4%.[6] Hypothyroidism can be easily detected by assessing serum thyroid stimulating hormone (TSH) levels. A slight increase in TSH levels with normal T3 and T4 indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T3 and T4 levels indicate clinical hypothyroidism. Elevated thyrotropin-releasing hormone levels due to hypothyroidism are often associated with increased prolactin (PRL) levels and a delayed LH response to GnRH.[7] It has been recommended that even in the presence of raised PRL levels, the treatment should be first given to treat hypothyroidism before evaluating other causes of raised PRL levels.

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Thyroid evaluation should be done in any woman who wants to get pregnant with family history of thyroid problem or irregular menstrual cycle or had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse. The comprehensive thyroid evaluation should include T3, T4, thyroid stimulating hormone (TSH), and thyroid autoimmune testing such as thyroid peroxidase (TPO) antibodies, thyroglobin/antithyroglobin antibodies, and thyroid stimulating immunoglobulin (TSI). Thyroid autoimmune testing may or may not be included in the basic fertility workup because the presence of thyroid antibodies doubles the risk of recurrent miscarriages in women with otherwise normal thyroid function. [8-9]

Measurement of TSH and PRL is routinely done as a part of infertility workup. Due to the lack of population-based infertility data of women with subclinical hypothyroidism in our state, we planned to study the prevalence of hypothyroidism in infertile women as well as to assess their response to drug treatment for hypothyroidism.

MATERIAL AND METHODS

The study was carried out in the Department of Obstetrics and Gynaecology at Government medical college, Jammu & Kashmir. The subjects were selected from the patients coming to endocrinology outpatient department (OPD) and gynaecology OPD. The study was approved by the Institutional Ethical Committee and was conducted after taking informed, written consent of the participants.

Reproductive age group (20 - 40 yrs.) and all infertile women of the above age group (both primary and secondary) included in study. Infertile women having tubular blockage, pelvic inflammatory disease, endometriosis on diagnostic laparoscopy or hysteroscopy and with genital TB (PCR-positive); with liver, renal or cardiac diseases; those already on treatment for thyroid disorders or hyperprolactinemia; Liver, renal, cardiac or any chronic systemic diseases; Any congenital anomaly of urogenital tract / obvious organic genital lesions also were excluded from the study.

Sample Size Estimation: The sample size determination has been done for the Chi-square test of independence using G*Power 3.1.9.2 statistical power analysis with a bio statistician's help. The minimum sample size came out as 122 to achieve the power of the test of 0.80 for 0.05 level of α. Therefore, the final sample size was 122

After informed consent, thyroid profile (serum TSH, T3, T4) of all subjects was done at their first visit. As per National Health and Nutrition Examination Survey III [10] 2002, the subjects were divided into three groups.

- Group 1 (euthyroid): Infertile women with normal TSH level (0.39–4.6 mIU/ml).
- Group 2 (subclinical hypothyroidism): Infertile women with raised TSH level ranging from 4.6–20 mIU/ml and normal free T4 level.
- Group 3 (overt hypothyroidism): Infertile women with TSH level > 20 mIU/ml and low free T4 level.
- As per WHO guidelines, PRL level > 25 µg/l is considered as hyperprolactinemia. [11]

Methods: Routine investigations such as random blood sugar (RBS), renal functions tests (RFT), hemogram, urine routine, and ultrasound (as and when required) were done. TSH and PRL were measured using chemiluminescence assay. The machine used for chemiluminescence was immulite 1000 (this is a test unit that contains an assay specific coated bead which serves as the reaction vessel for sample processing).

Statistical Analysis: The collected data was entered in MS Excel sheet and will be imported in IBM SPSS 24.0 software. The collected data was analyzed by appropriate statistical tools, techniques & tests such as Mean (+/-) SD, graphical representation of data, frequency distribution, Chi-Square test, ANNOVA etc. A $P < 0.05$ was considered as statistically significant.

RESULTS

Of the 122 infertile women enrolled for the study, 2 were excluded due to microprolactinoma and endometriosis. Of the remaining 120 women, 69 (57.5%) were hypothyroid while 51 (42.5%) were euthyroid. Of 69 hypothyroid women, 58 (48.3%) had subclinical hypothyroidism and 11 (9.16 %) had overt hypothyroidism. Among 69 subclinical hypothyroid infertile women, 48 (69.5%) women conceived after 6 weeks to 3 months of therapy and 18 (14.5%) women conceived after 3 months to 1 year of therapy. None of the overtly hypothyroid women conceived after treatment with levothyroxine. The mean time to conception was 14.56 ± 4.83 months.

As presented in Table 1, age did not differ significantly across the groups categorized by thyroid status ($P > 0.05$). However, a significant difference in body mass index was observed between infertile women with hypothyroidism and those with normal thyroid function ($P < 0.05$).

Table 1: Baseline demographic variables of study participants

Variable	Euthyroidism (n=51)		Subclinical hypothyroidism (n=58)	Overt hypothyroidism (n=11)	P Value
	Tab Negative (n=45)	Tab Positive (n=6)			
Age (years); Mean ± SD	24.55 ± 2.84	26.88 ± 5.56	24.59 ± 3.52	26.39 ± 5.73	0.75
BMI (kg/m²); Mean ± SD	26.77 ± 3.73	24.28 ± 3.66	28.58 ± 5.54	35.79 ± 4.41	<0.05*

*=Statistically significant

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As illustrated in Table 2, the mean TSH level was higher among study participants with overt hypothyroidism (32.94±3.67), followed by those with subclinical hypothyroidism (8.49±3.07). A significant difference in TSH levels was observed between infertile women across the different thyroid status groups ($P < 0.05$). Additionally, the mean prolactin levels also differed significantly among the groups categorized by thyroid status ($P < 0.05$), with subclinical hypothyroidism showing a mean prolactin level of 15.16±10.15 and overt hypothyroidism showing a mean prolactin level of 15.47±8.97.

Table 2: Baseline clinical parameter of the study participants (n=120) has been shown in the following tabulation

Variable	Euthyroidism (n=51)		Subclinical hypothyroidism (n=58)	Overt hypothyroidism (n=11)	P Value
	Tab Negative (n=45)	Tab Positive (n=6)			
Primary infertility (%)	100	100	47.9	100	>0.05
Secondary infertility (%)	0	0	62.1	0	-
Mean TSH (mIU/L)	2.67±0.95	2.66±0.99	8.49±3.07	32.94±3.67	<0.05*
Mean T4 (nmol/L)	103.55±17.27	103.77±16.57	106.82±22.61	101.33±6.11	0.65
Mean prolactin (µg/L)	6.69±2.69	6.66±2.59	15.16±10.15	15.47±8.97	<0.05*
Hyperprolactinemia (%)	0	0	22.9	0	-
TPOAb (%)	0	100	100	0	-
TgAb (%)	0	50	60.4	0	-

TSH: Thyroid stimulating hormone, BMI: Body mass index, TPOAb: Thyroid peroxidase antibody, TgAb: Thyroglobulin antibody. *=Statistically significant

DISCUSSION

Thyroid hormones have profound effects on reproduction and pregnancy. Thyroid dysfunction is implicated in a broad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility [12-13]. Hypothyroidism is associated with increased production of TRH, which stimulates pituitary to secrete TSH and PRL. Hyperprolactinemia adversely affects fertility potential by impairing GnRH pulsatility and thereby ovarian function [14-15]. Gynaecologists mostly check TSH and PRL levels in every infertile female, regardless of their menstrual rhythm.

The prevalence of subclinical hypothyroidism was more common than overt hypothyroidism in this investigation, aligning with findings from Verma et al. [16], Biradar et al. [17], and Rijal et al. [18]. The prevalence of hyperprolactinemia was higher in Iraq (60%) and even in Hyderabad, India, it is higher (41%) as compared to the present study in North India. Hyperprolactinemia may result from stress, and the variable prevalence may be due to the different stress levels in different areas. [9,19]

The average time to conception (approximately 14 months) exceeded that reported by Raber et al. [7]. Elevated TSH levels were linked to a lower conception rate, in line with Raber et al. [7] and Gerhard et al. [20].

Age did not significantly differ among the various groups based on thyroid status ($P > 0.05$). However, a notable difference in body mass index was observed in infertile women with hypothyroidism compared to those with normal thyroid levels ($P < 0.05$), consistent with Rahman et al. [21].

The percentage of conception in euthyroid women who were positive for antithyroid antibodies was 50% after levothyroxine treatment. Of these, 50% had miscarriage and rest 50% continued with their pregnancy. The result of the present study was not consistent with Negro et al. [22] who reported that the pregnancy rate was not affected either by the presence of antithyroid antibodies or treatment with levothyroxine.

The percentage of abortion in hypothyroid infertile women who conceived with the help of levothyroxine was 31.3%, and 80% of those aborted women were positive for thyroid antibodies. Increased number of abortions was noted in this study when compared to Raber et al. [7] and Rahman et al. [21] The association between thyroid antibodies and abortions could be made out in this study.

Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones. [14,23] It has been recommended that in the presence of raised TSH along with raised PRL levels, the treatment should be first to correct the hypothyroidism before evaluating further causes of hyperprolactinemia. Hormone therapy with thyroxine is the choice of treatment in established hypothyroidism. It normalizes the menstrual cycle, PRL levels and improves the fertility rate. Therefore, with simple oral treatment for hypothyroidism, 76.6% infertile women with hypothyroidism conceived after 6 weeks to 1 year of therapy. We tried to maintain normal TSH levels; compliance and adequacy of hypothyroid drug dose were checked by TSH measurement after 6 to 8 weeks interval.

Therefore, the normal TSH levels are the pre-requisite requirements for fertilization. The decision to initiate thyroid replacement therapy in subclinical hypothyroidism at early stage is justified in infertile women. Our data also indicate that variations in TSH

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levels in the narrower range or borderline cases, i.e. 4–5, 5–6, and >6.0 μIU/ml, should not be ignored in infertile women which are otherwise asymptomatic for clinical hypothyroidism. This group of infertile women, if only carefully diagnosed and treated for hypothyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures. For better management of infertility cause, we should plan further studies with the large sample size and long-term follow-up which are necessary to validate the variation in TSH and PRL levels.

CONCLUSION

Hypothyroidism is an important emerging cause of female infertility and thus, the decision to initiate treatment with levothyroxine in subclinical hypothyroidism at an early stage is justifiable in infertile women. Our data also suggests that women with normal TSH levels who are positive for thyroid antibodies should be treated with levothyroxine. Women who want to conceive should be screened for serum TSH, T3, T4 and thyroid antibodies particularly thyroid peroxidase antibody and thyroglobulin antibodies in their infertility work up.

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