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Research Article

Prevalence of subclinical and overt hypothyroidism in infertile women

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ABSTRACT

Background: Hypothyroidism has a significant effect on fertility causing anovulatory cycles, luteal phase defect, hyperprolactinemia and sex hormone imbalances. To identify potential and overt hypothyroidism, thyroid screening should be done for all infertile women. The objective of the study was to find the prevalence of subclinical and overt hypothyroidism among infertile women, to find the correlation of hypothyroidism with hormonal and metabolic parameters associated with infertility.
Methods: Hospital based analytical cross sectional study was conducted for one and half years among 300 infertile women with primary and secondary infertility. Women with primary and secondary infertility. All hypothyroid women on thyroxine supplementation, male factor infertility, female factor infertility like tubal factor, anomalies of the urogenital tract, obvious organic lesions in the pelvis and women unwilling to participate or sign the informed consent.
Results: The prevalence of hypothyroidism in infertile women was 27%. Among them, 25% were subclinical hypothyroid and 2.33% overt hypothyroid. Menstrual dysfunction was observed in 52% of subclinical and 51.15% of overt hypothyroid women, predominant type being oligomenorrhea. We found a negative correlation of hypothyroidism with the family history of thyroid disease. 91.4% of hypothyroid infertile women were obese and the association was strongly significant. Prevalence of hyperprolactinemia in infertile women was 24.67%. The association of hyperprolactinemia with hypothyroidism was 23%. Raised LDL levels were observed in 80% of subclinical and 100% overt hypothyroidism infertile women.
Conclusions: Hypothyroidism alters the Hypothalamo-Pituitary ovarian axis and is one of the important etiological factors of female infertility. Most of the women were asymptomatic. Hence every infertile woman should be screened for thyroid profile to open better prospects of conception.

Keywords: Subclinical hypothyroidism, Overt hypothyroidism, Hyperprolactinemia

INTRODUCTION

Thyroid dysfunction is one of the important hormonal factors contributing to female infertility. The prevalence of hypothyroidism varies between 2 - 4 % in women of reproductive age group.[1,2] It has profound effect on estrogen metabolism, menstrual function and fertility causing anovulatory cycles, luteal phase defect, hyperprolactinemia and sex hormone imbalances. Thyroid evaluation should be done in women who are unable to conceive after 1 year of unprotected intercourse, those with irregular menstrual cycles or recurrent miscarriages or family history of thyroid disorders. Hypothyroidism can be easily detected by estimating thyroid stimulating hormone (TSH) levels in the blood. A slight increase in TSH levels with normal T_3 (tri iodothyronine) and T_4 (thyroxine) indicates subclinical hypothyroidism (SCH) whereas high TSH levels with low T_3 and T_4 levels indicate overt hypothyroidism. SCH is more common and often asymptomatic. Hypothyroid infertile women are associated with hyperprolactinemia due to increased

production of thyrotropin releasing hormone (TRH) which further increases the level of TSH as well as prolactin. The aim and objective of the study was to find the prevalence of hypothyroidism in female infertility, associated risk factors and correlation with other hormonal and biochemical factors so that identifying the problem at the earliest and simple oral treatment with L-Thyroxine would cause a great benefit for hypothyroid infertile patients.

METHODS

Study design

Hospital based analytical cross sectional study

Study period

One and half years from April 2014 to September 2015 .

Study population

300 women who attend the outpatient department, OBGY, ACS Medical College, Chennai.

Inclusion criteria

Women with primary and secondary infertility.

Exclusion criteria

1. All hypothyroid female patients who were on L-thyroxine supplementation.
2. Male factor infertility, female factors like tubal factor, urogenital tract anomalies and obvious organic lesions in the pelvis.
3. Women unwilling to participate or sign the informed consent.

Ethical considerations

Informed consent was obtained from all the participants at the start of the study. Ethical clearance was taken from the institutional ethical committee before starting the study.

Proforma

Detailed clinical history was taken and clinical examination performed. Information about age, menarche, menstrual cycles, marital status, clinical features of hypothyroidism, family history of thyroid disease, anthropometric measurements of weight, height, BMI were noted. Semen analysis, USG abdomen and pelvis, hysterosalpingography, premenstrual endometrial sampling, serum TSH and free T_4 levels by radio immuno assay (RIA), serum prolactin levels and lipid profile were done.

Regarding hypothyroidism, the women were divided into 3 groups, as per the National Health and Nutrition Examination Survey III 2002.[3]

1. Group 1 (euthyroid): Infertile women with normal TSH level (0.39-4.6 mIU/ml).
2. Group 2 (subclinical hypothyroidism): Infertile women with raised TSH level ranging from 4.6-20 mIU/ml and normal free T_4 level.
3. Group 3 (overt hypothyroidism): Infertile women with TSH level > 20 mIU/ml and low free T_4 level.

With regard to raised prolactin (PRL) levels, as per WHO guidelines, PRL level > 25 µg/l was considered as hyperprolactinemia.[4]

BMI - ICMR Guidelines (2008)[5]

1. Normal - 18 - 22.9 kg/m^2
2. Overweight - 23 - 25 kg/m^2
3. Obese - > 25 kg/m^2

In our study, we have analysed the prevalence of hypothyroidism among primary infertile and secondary infertile women, potential demographic risk factors, hormonal and metabolic parameters associated with hypothyroidism.

Categorical data were analysed with the odds ratio, chi square test and the P value of < 0.05 was considered statistically significant. SPSS software was used for statistical analysis.

RESULTS

Table 1: Socio - demographic risk profile of infertile women.

Variable	Classification of variable	No. of pts. (300)	Percentage %
Age	≥18-25	106	35.33
	25-30	128	42.67
	30-35	57	19.00
	>35	9	3.00
BMI	<23	161	53.67
	23-25	61	20.33
	>25	78	26.00
Family H/o	Yes	25	8.33
	No	275	91.67
Altered Lipid Profiles (Raised LDL)	Yes	69	23.00
	No	231	77.00

Thyroid profile and prevalence of subclinical and overt hypothyroidism among infertile women

Among 300 women with infertility, 73 % of the patients were euthyroid and 27% (82 patients) were hypothyroid with 95% C.I: 22.29 – 32.37 (Figure 1).

The prevalence of subclinical hypothyroidism was 25% (75 patients) and overt hypothyroidism was 2.33% (7 patients) which suggests that SCH was more common than overt hypothyroidism among infertile hypothyroid group.

The percentage of SCH and overt hypothyroidism women among primary infertile group were 27.62% and 2.51% and among secondary infertile group were 14.65% and 1.64 % respectively. This data shows that hypothyroidism was observed relatively more common in primary infertile women (Figure-2).

Table 2: Clinical and biochemical profile of infertile patients.

Variables	Number	Percentage	95% CI
Hypothyroidism (TSH > 4.6)	82	27.33	22.29-32.37
Anovulatory menstrual cycles	74	24.67	19.79-29.55
Obesity	78	26	21.04-30.96
Hyperprolactinemia	74	24.67	19.79-29.55
Altered Lipid Profile	69	23	18.24-27.76

Socio-demographic factors of infertile women

Age

Most of the study subjects belong to the age group of 25 - 30yrs (42.67%) followed by 18-25 yrs (35.33%), 30-35 yrs (19%) and > 35 yrs (3%). Women of < 25 yrs of age group had 1.25 fold increased risk of hypothyroidism in our study (Odds' ratio [OR] 1.25; 0.74 – 2.11) but this demographic variable was not found to be a risk factor for hypothyroidism (P = 0.49) as seen in Table 3.

Family history of Thyroid dysfunction

8.33% (25 patients) of infertile women (Table 1) showed positive family history of thyroid disorder. Among hypothyroid group, only 2 patients out of 82 (2.67% - subclinical, nil-overt hypothyroidism patients) were having family history of thyroid dysfunction.

In contrary to the various studies which shows that family history is one of the risk factors for hypothyroidism, our statistics showed a negative correlation between family history of thyroid disease and hypothyroidism (OR - 4.72; 95% C.I – 1.09 -20.48) which was statistically significant (P =0.04) as seen in Table -3.

BMI and obesity

26% of the study group (95% C.I: 21.04 – 30.96) were obese (BMI >25). We found a high incidence of obesity 91.4% (75 patients out of 82) among hypothyroid women with a strong correlation (OR - 767.86 (193.60 - 3045.56)) and a statistically significant P value 0.0000000 (Table 3).

Menstrual dysfunction

24.67% of infertile women were found to have irregular menstrual cycles. Among hypothyroidism group, 52% of subclinical hypothyroid women had menstrual dysfunction, most common being oligomenorrhea (33.33%) followed by menorrhagia (18.67%). In overt hypothyroidism group, irregular cycles were observed in 51.15%, principle menstrual abnormality being oligomenorrhea (28.57%) followed by menorrhagia (14.29%) and amenorrhea (14.29%). Among the euthyroid infertile women, only 14.22% had menstrual dysfunction (Figure-2). A strong positive correlation of menstrual dysfunction/anovulatory cycles and hypothyroidism with OR - 6.65; 95% C.I: 3.74 – 11.84 was found with a statistically significant P value (0.0000000) as seen in Table 3.

Prolactin levels

Hyperprolactinemia (>25 mg/ml) was observed in 24.67 % (74 out of 300 patients) of the study population with 95% C.I: 19.79 – 29.55 (Table 2). When the correlation of raised prolactin levels and hypothyroidism women was analysed, 23% (19 out of 82 patients) of hypothyroid women were found to have hyperprolactinemia. The above data suggests that not only women with hypothyroidism, but also euthyroid women with infertility were associated with hyperprolactinemia. Statistical analysis in our study showed that hypothyroidism was 1.2 times common in women with normal prolactin levels than in women with hyperprolactinemia. (OR - 1.19; 95% C.I: 0.62 -2.03) and the statistical correlation of hypothyroidism with raised PRL was insignificant. (P = 0.83)

Altered lipid profile

Hypothyroidism is associated with hyperlipidemia. When we studied the association of raised LDL levels with the study group, 23% of women (18.24 – 27.76) had raised LDL levels. Among hypothyroidism group, raised LDL levels were observed in 80% of subclinical and 100% of overt hypothyroidism patients. Strong association of hyperlipidemia with hypothyroidism was observed with OD - 482.4; 95% C.I: 107.57 – 2163.43 having a highly significant P value of 0.0000000 (Table 3).

DISCUSSION

Hypothyroidism is one of the important endocrinological disorders causing ovulatory dysfunction and infertility in reproductive age group women. Most of the subjects in the study group belonged to 20 - 30 years of age.

Various studies have been conducted regarding the prevalence of hypothyroidism in infertile women. Indu Verma et al study on 394 infertile women showed 23.9% (94 patients) prevalence of hypothyroidism in which SCH and overt hypothyroidism were 15% (59) and 8.8% (35 patients) respectively.[6] In Dilruba Rahman et al study on 30 subfertile women, the proportion of women suffering from hypothyroidism was 33.3% (SCH - 26.7%, overt hypothyroidism - 6.7%).[7] In Mohana Priya et al study on 98 infertile women, 53.7% were hypothyroid (50.5% - SCH and 3.2% - overt hypothyroidism).[8] Raber's W et al study showed SCH in 34% of infertile women and in Bals-Pratsch M et al study it was 25%.[9,10] In our study, the prevalence of SCH was 25% (75 patients) and overt hypothyroidism was 2.33% (7 patients).

Table 3: Correlation between clinical, demographic and biochemical characteristics in infertile patients and subclinical and overt hypothyroidism.

Variable	Classification of variable (Total number in the group)	No. of SCH and overt hypothyroidism	Chi-square value	Odds ratio (95% C.I of odds ratio)	P value
Age	≤ 25 years (106) > 25 years (194)	32 50	0.47	1.25 (0.74 – 2.11)	0.49
Family history of thyroid disorders	No (275) Yes (25)	80 2	4.13	4.72 (1.09 – 20.48)	0.04*
Obesity	Yes (78) No (222)	75 7	250.51	767.86 (193.60 - 3045.56)	0.0000000*
Anovulation	Yes (74) No (226)	43 39	44.3	6.65 (3.74 – 11.84)	0.0000000*
Prolactin levels	Normal (226) Increased (74)	63 19	0.05	1.19 (0.62 – 2.03)	0.83
Altered Lipid profile (Raised LDL)	Yes (69) No (231)	67 15	219.6	482.4 (107.57 - 2163.43) (0.62 – 2.03)	0.0000000*

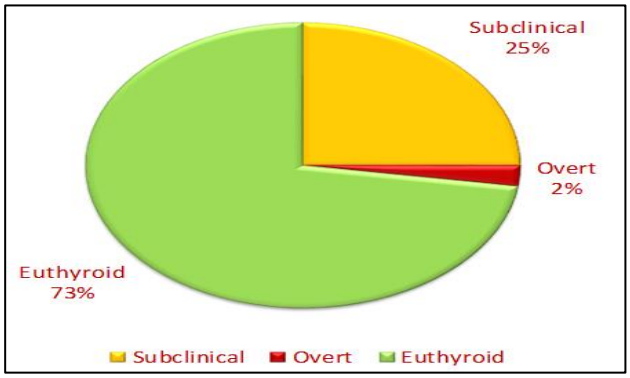

Figure 1: Prevalence of hypothyroidism among infertile women.

Most of the studies and literature review suggest that the prevalence of SCH was more common than overt hypothyroidism among infertile women. SCH may progress to overt hypothyroidism and the rate of progression. The rate of progression would be higher among women with higher levels of TSH or presence of TPO-Ab.[1] Even though there was a controversy regarding treatment of SCH, maintaining TSH levels at the lower end of normal may improve the pregnancy rates among infertile women and reduce the risk of miscarriages.

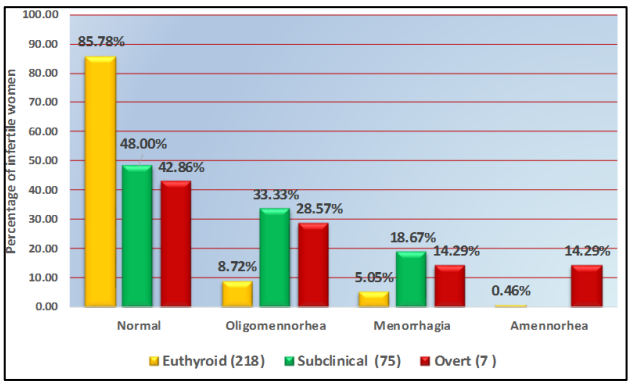

Figure 2: Menstrual patterns in infertile women.

Anovulatory cycles were very common in hypothyroid infertile women. In Acharya Neema et al study, 60.87% of subclinical hypothyroid women (oligomenorrhea -

28.2%, menorrhagia -17.39%) and 52.95% of overt hypothyroid women had menstrual dysfunction (oligomenorrhea - 23.5%, menorrhagia -17.64%).[12] In another study conducted by Joshi et al, prevalence of menstrual abnormality was found to be 68% among 22 hypothyroid patients, mainly oligo/hypomenorrhoea even though all types of bleeding abnormalities were present, In Krassas et al study, 23% among 171 hypothyroid patients had menstrual dysfunction, predominantly oligomenorrhea and less commonly secondary amenorrhea.[13,14] In our study, 52% of subclinical, 51.15% of overt and 14.22% of euthyroid women had menstrual dysfunction, predominant type being oligomenorrhea (Figure 2).

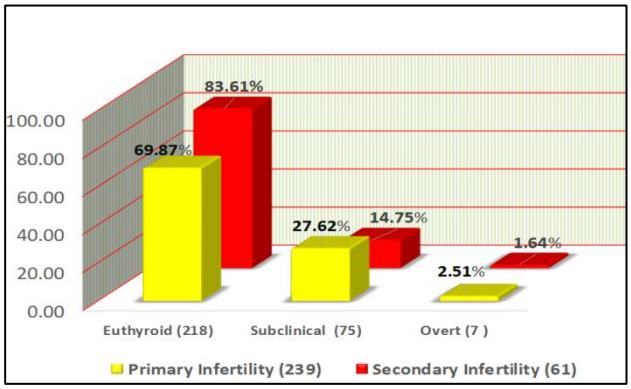

Figure 3: TSH values in patients with primary and secondary infertility.

The relation between hypothyroidism and menstrual dysfunction was mediated by increase in thyrotropin-releasing hormone (TRH) thus interfering the regulation of ovarian function. In addition it alters the peripheral metabolism of oestrogen by decreasing sex hormone-binding globulin production, increase in prolactin levels and altered GnRH pulsatile secretion causing inadequate corpus luteum due to delay in LH response contributing to anovulation.

Subclinical and overt hypothyroidism is frequently associated with weight gain, decreased thermogenesis, and metabolic rate. In Mario Rotondi et al study on hypothyroidism associated with obesity, subclinical hypothyroidism was observed in 13.7% obese patients.[15] Verma et al study on 625 hypothyroid patients found 34% (26) obesity among 77 subclinical hypothyroid patients and 46% (252) obesity among 548 overt hypothyroid patients.[16] In our study, 69 out of 72 (92%) subclinical hypothyroid patients and 6 out of 7 overt hypothyroid patients (82.71%) were obese.

As hypothyroidism is related to obesity, to avoid obesity related metabolic changes (hypertension, dyslipidemia, insulin resistance), in such patients, apart from thyroid hormone therapy, life style interventions should be advised.

Hypothyroidism is associated with hyperprolactinemia. In Indu Verma et al study on 394 infertile women for the prevalence of hypothyroidism, 54 women (13.7%) were having hyperprolactinemia and 18 patients (4.57%) had both hypothyroidism and hyperprolactinemia.[6] Binita Goswami et al study on 160 women with primary infertility showed hyperprolactinemia in 41% of infertile women and 46.1% of hypothyroid women were associated with hyperprolactinemia.[17] The underlying mechanism for raised PRL levels is, hypothyroidism stimulates the production of TRH which is associated with increased production of TSH and prolactin. Hyperprolactinemia impairs GnRH pulsatality leading to anovulation and infertility. In our study, 24.67% of infertile women had raised prolactin levels and 23% of women were having hypothyroidism associated with hyperprolactinemia.

The data suggests that it is important to estimate both serum TSH and prolactin levels in the infertility work up. In hypothyroid infertile women associated with hyperprolactinemia, before evaluating further causes of raised PRL levels, the first treatment should be to correct the hypothyroidism.

Hypothyroid women are at risk of hyperlipidemia. Significant increase in LDL oxidation occurs in hypothyroid patients, the degree of which is directly related to the serum LDL cholesterol concentration. A study conducted by Zha K et al on LDL in patients with SCH found that serum LDL-C level were higher in SCH group than in euthyroid group ($P < 0.05$).[18] Staub et al study on euthyroid (52) and hypothyroid women (SCH - 69, overt hypothyroidism - 17) observed an elevated serum LDL cholesterol levels in 42.9% of patients with hypothyroidism compared with 11.4 % in control group.[19] In our study, 23% of infertile women had raised LDL levels. Among hypothyroid infertile patients, 80% of subclinical and 100% of overt hypothyroid patients had raised LDL levels.

CONCLUSION

The prevalence of hypothyroidism in infertile women is much higher than in women with reproductive age group. Subclinical hypothyroidism is more prevalent than overt hypothyroidism. Menstrual dysfunction and the proportion of obese women were found to be significantly high in the study. Screening for hypothyroidism is extremely important so that treatment with thyroxine can be started at the earliest so as to maintain TSH levels at the lower limit in the management of subfertility and recurrent miscarriages. As hypothyroidism is associated with hyperprolactinemia, measurement of PRL should also be done as a part of infertility work up and correction of hypothyroidism should be done first. Hyperlipidemic patients with hypothyroidism should be treated with thyroxine as restoration of euthyroidism can effectively improves the lipid levels.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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